The American Journal of Medicine

November 1953

The American Journal of Medicine

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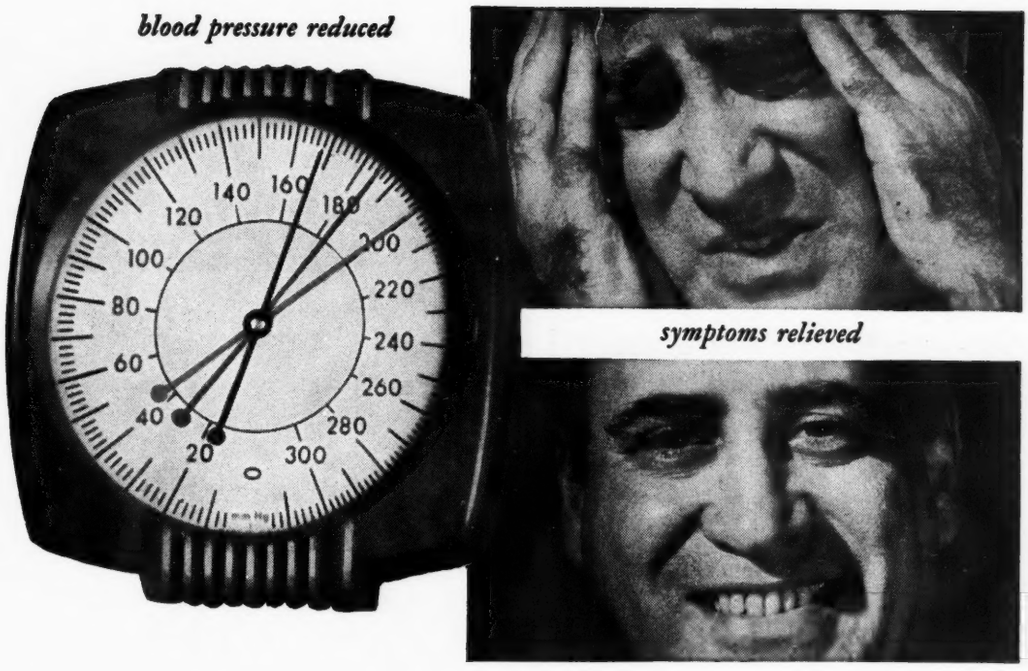
blood pressure reduced



symptoms relieved

A drug of choice for long term oral treatment of hypertension . . . *found effective in 81% of patients*[1]

Lower blood pressure has been obtained in 81% of moderate and severe hypertensives treated with hexamethonium chloride (available as Methium) under general-practice conditions.[1] In 60% of these patients lower pressures continued for 4 to 16 months of the study.

Also, as pressure is reduced, improvement is almost universally seen in eye and heart symptoms, headache, vertigo, dyspnea, etc.[1-6] In some cases even where pressure fails to respond, symptoms may nonetheless abate.[4-7]

Methium, a potent autonomic ganglionic blocking agent, reduces blood pressure by interrupting nerve impulses responsible for vasoconstriction. Because of its potency, careful use is required. Pre-treatment patient-evaluation should be thorough. Special care is needed in impaired renal function, coronary artery disease and existing or threatened cerebral vascular accidents. *A booklet of complete instructions for prescribing is available and should be consulted prior to initiating therapy.*

1. Moyer, J. H., et al.: Am. J. M. Sc. *225*:379 (April) 1953.
2. Mills, L. C., and Moyer, J. H.: A.M.A. Arch. Int. Med. *90*:587 (Nov.) 1952.
3. Frankel, E.: Lancet *1*:408 (Feb. 17) 1951.
4. Johnson, I., et al.: Texas State J. M. *48*:331 (June) 1952.
5. Council on Pharmacy and Chemistry: J.A.M.A. *151*:385 (Jan. 31) 1953.
6. Grimson, K. S., et al.: J.A.M.A. *149*:215 (May 17) 1952.
7. Turner, R.: Lancet *1*:1217 (June 2) 1951.

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(BRAND OF HEXAMETHONIUM CHLORIDE)

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has proved to be the most valuable remedy for the control of chronic hypoparathyroidism and by its use patients may be kept free of the symptoms of tetany as well as of the trophic manifestations of chronic hypocalcemia."*

Orally administered, Hytakerol facilitates the absorption of calcium from the bowel and increases the excretion of phosphate by the kidney.

Sulkowitch's simple urinary test may be used instead of repeated blood analyses in checking calcium levels.*

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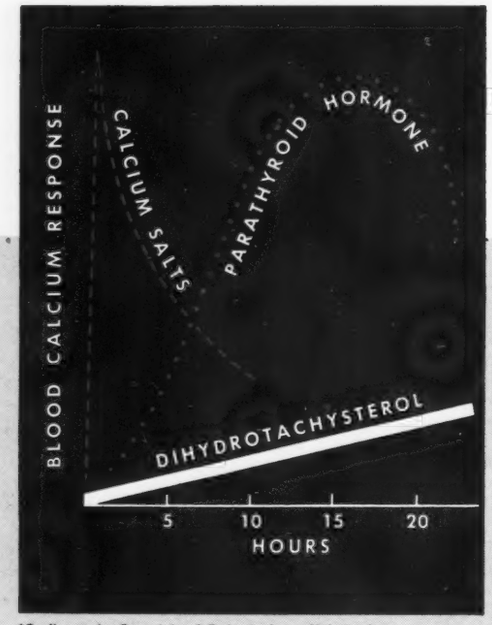
Brand of
Dihydrotachysterol



*Grollman, A.: Essentials of Endocrinology. Philadelphia, J. B. Lippincott Co., 1947, 2nd ed., p. 269

Winthrop-Stearns INC.
New York 18, N. Y. Windsor, Ont.

DOSE

Orally from 3 to 10 cc. (or from 6 to 20 capsules) daily until tetany is relieved; weekly maintenance dose from 1 to 7 cc. (or from 2 to 14 capsules) depending upon the blood and urine calcium levels. From 10 to 15 Gm. calcium lactate or gluconate may be given daily as supplement through the period of therapy.

SUPPLIED

Hytakerol in Oil, bottles of 15 cc.
Hytakerol Capsules (each equivalent to 0.5 cc.), bottles of 50.

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Clinical Studies

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refreshing
comfort
for patients
with
cold
grippe
flu

new

APAMIDE-VES

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analgesic-
antipyretic

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every patient with essential hypertension is a candidate for RAUDIXIN treatment

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step 1

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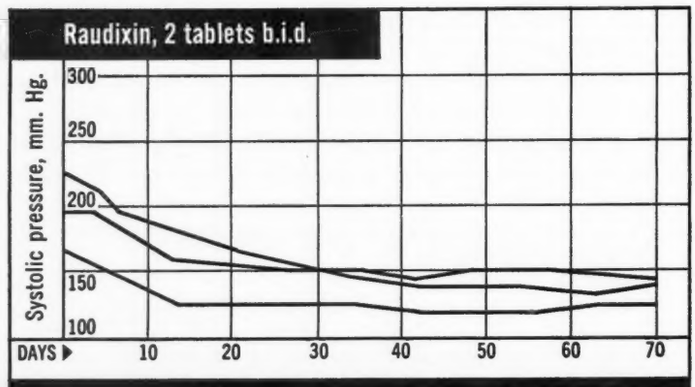
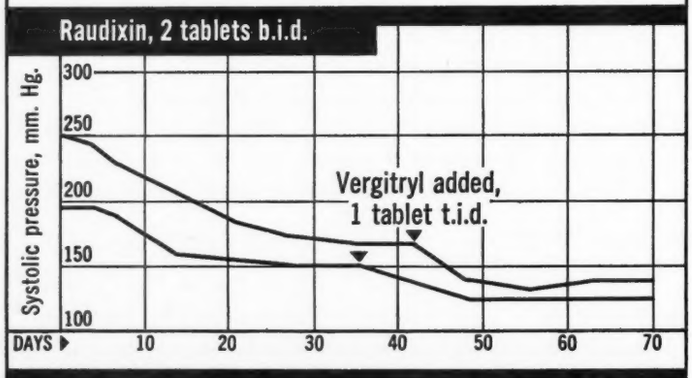


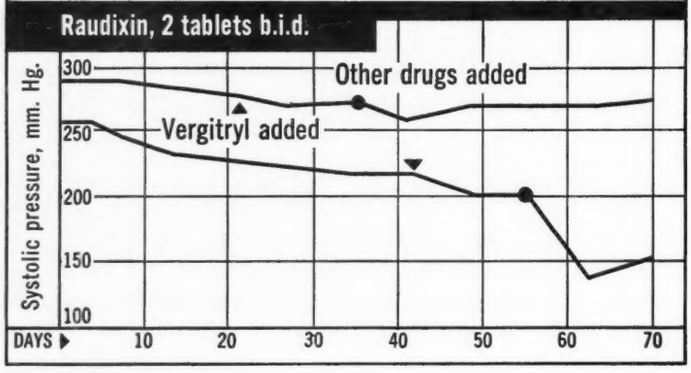
step 2

If blood pressure is not adequately controlled in four to eight weeks, Vergitryl (veratrum) may be added to Raudixin. This brings many of the remaining patients under control. Raudixin tends to delay tolerance to Veratrum, and makes smaller dosage possible.



step 3

For the few patients resistant to this combined regimen, a more potent drug may be added, for example, Bistrium (hexamethonium). The most potent drugs, which are potentially dangerous, are thus used only as a last resort in the most refractory cases.



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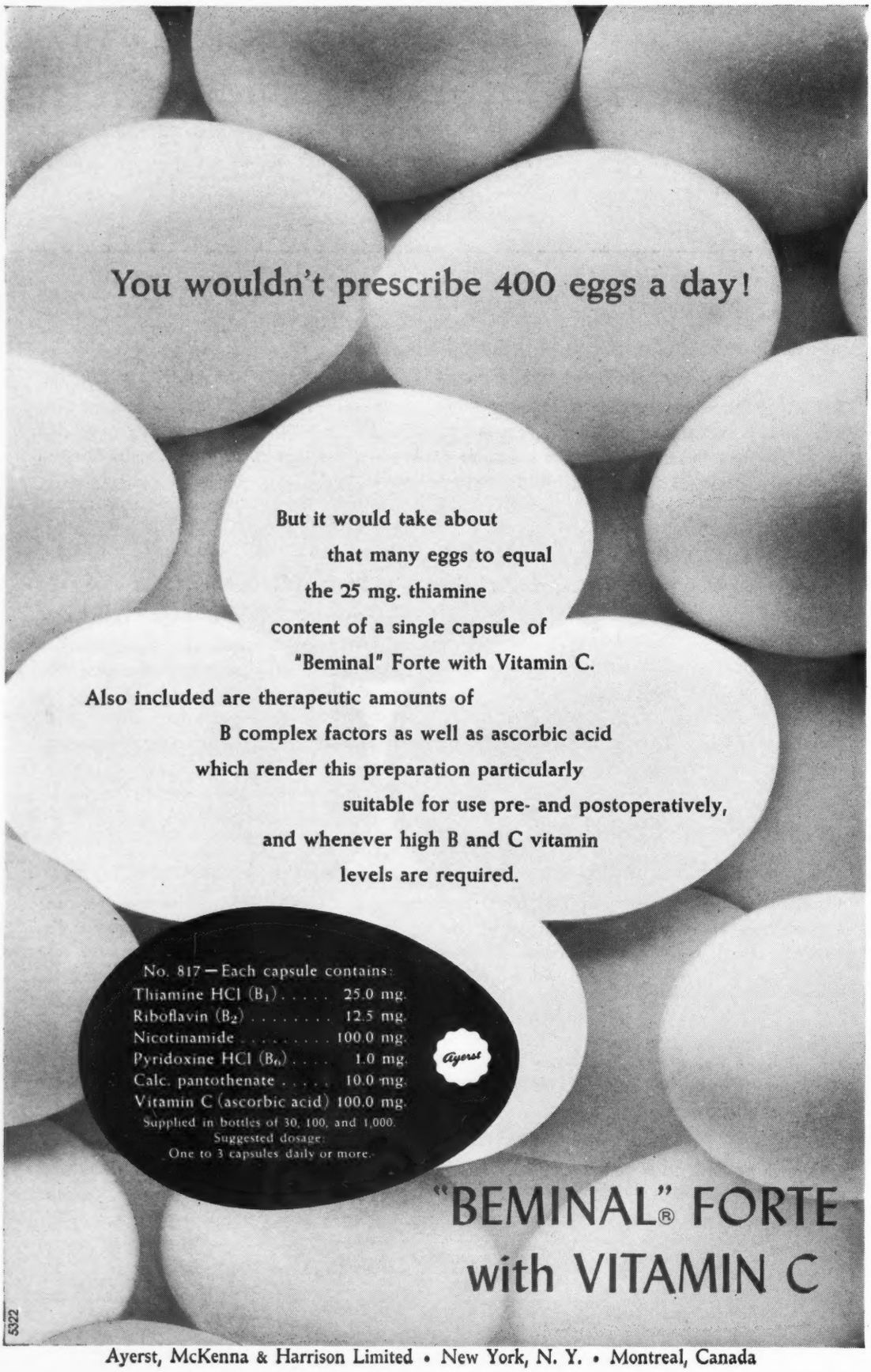

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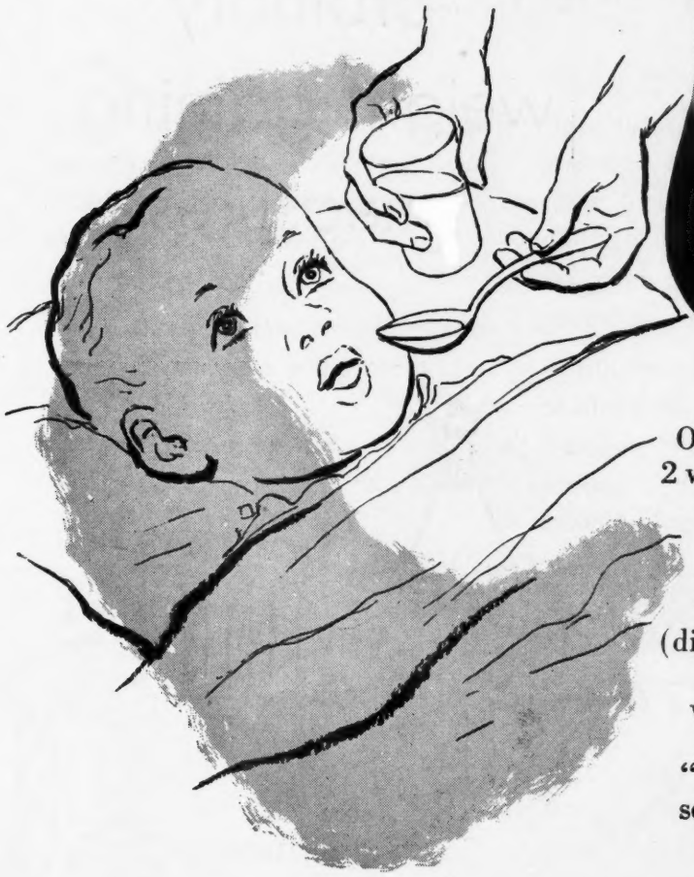
citrus is virtually

NON-ALLERGENIC



TYPICAL PATCH TEST

Over 400 infants and children from 2 weeks to 6 years of age acted as test subjects to check the incidence of sensitivity to orange juice. After 2 to 12 months' observation,* "no disturbance of bowel function (diarrhea or constipation) that could be attributed to the orange juice" was found. Also, the occurrence of regurgitation and rashes was "minimal". In the rare instances of sensitivity, care exercised by gentle reaming of juice (or the use of frozen concentrate) to avoid contamination with peel oil usually obviates the difficulty.

**J. Pediat. 39:325, 1951*

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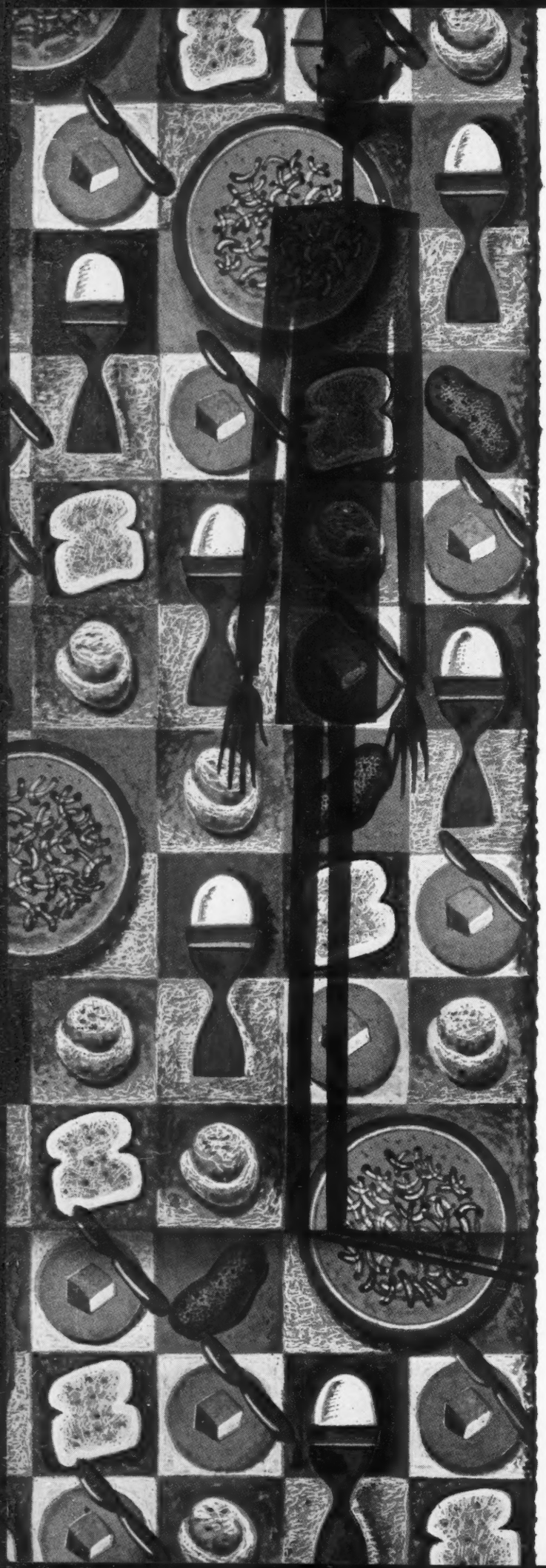
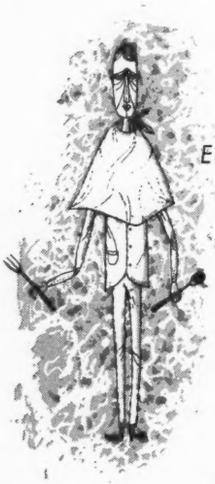


For the
many patients
resistant to
ordinary
weight gaining
measures



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A HORSE BUT...
THIN

DEBILITATED
AND...
THIN

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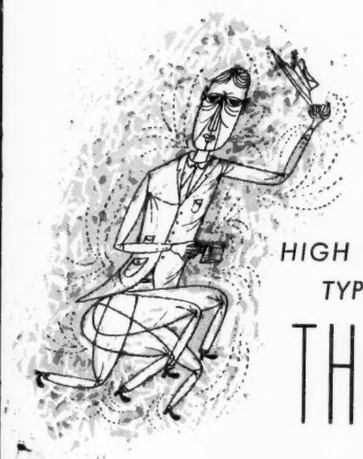


HIGH TENSION TYPE AND...

THIN

EMOTIONALLY DISTURBED AND...

THIN

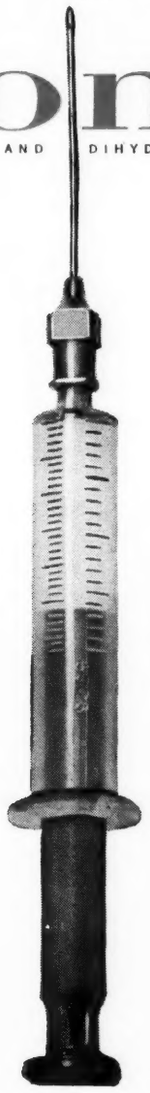
*Trademark of Schenley Laboratories, Inc.

a new advance in the control of tuberculosis

Drug therapy for the management of tuberculosis continues to advance at a rapid pace. In keeping with the latest improvement—which promises a substantially lower incidence of vestibular and auditory toxicity—Pfizer has made available a new combination of streptomycin and dihydrostreptomycin—

Combistrep*

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN COMBINATION



Recent clinical studies[1] have shown that such a combination, one-half streptomycin and one-half dihydrostreptomycin, gave rise to a significant reduction in neurotoxic side effects as compared to equivalent dosage of either drug used alone, even though administered over the prolonged treatment periods required for the control of tuberculosis.

Combistrep offers these benefits to the tuberculous patient with the further assurance that its purity is of the same high standard typical of all Pfizer pharmaceuticals.

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1. Heck, W. E.: Reduced Ototoxicity by Combined Streptomycin-Dihydrostreptomycin Treatment of Tuberculosis, Scientific Exhibit 317, 102nd Annual Meeting A.M.A., New York, June 1-5, 1953.

also,

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Streptohydrazid*—a crystalline compound combining streptomycin and isoniazid

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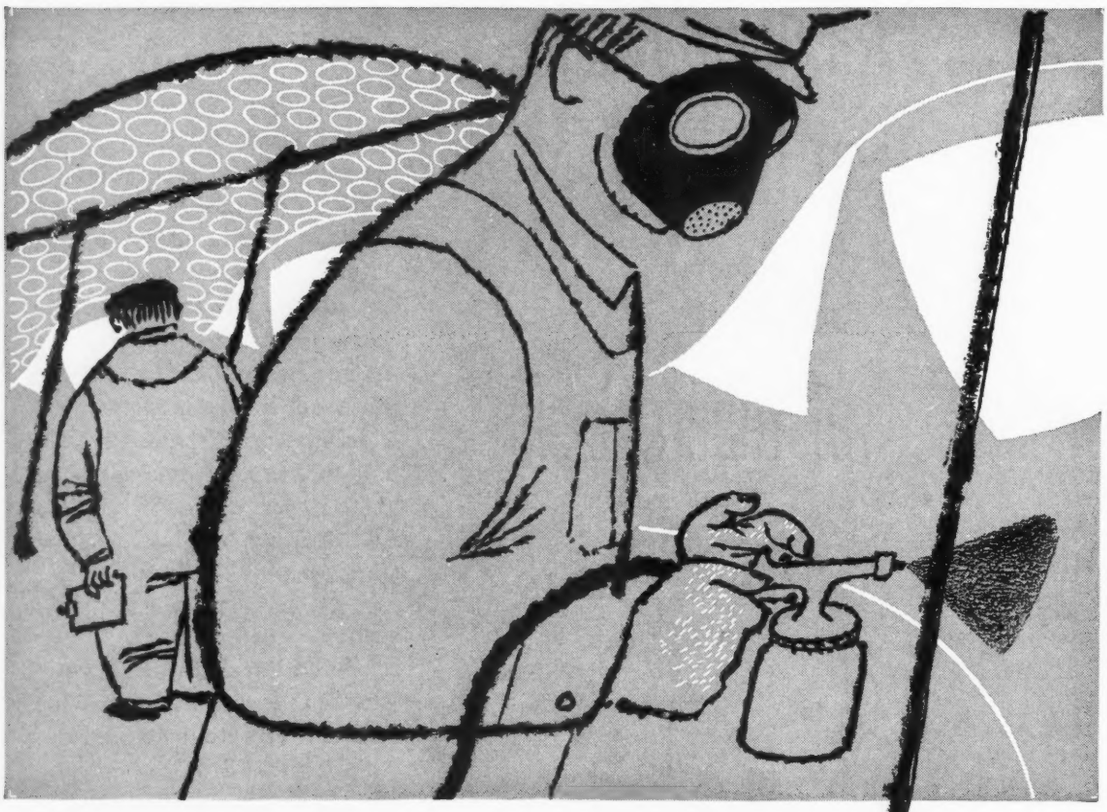

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NOT removed by ordinary washing, COVICONE Cream offers the long-lasting qualities often desired in the management of industrial and allergic dermatoses. An entirely new formula, COVICONE is a special *plasticized* combination of silicone, nitrocellulose and castor oil. Applied to the skin, it forms an effective but invisible physical barrier against sensitizing and irritating agents.

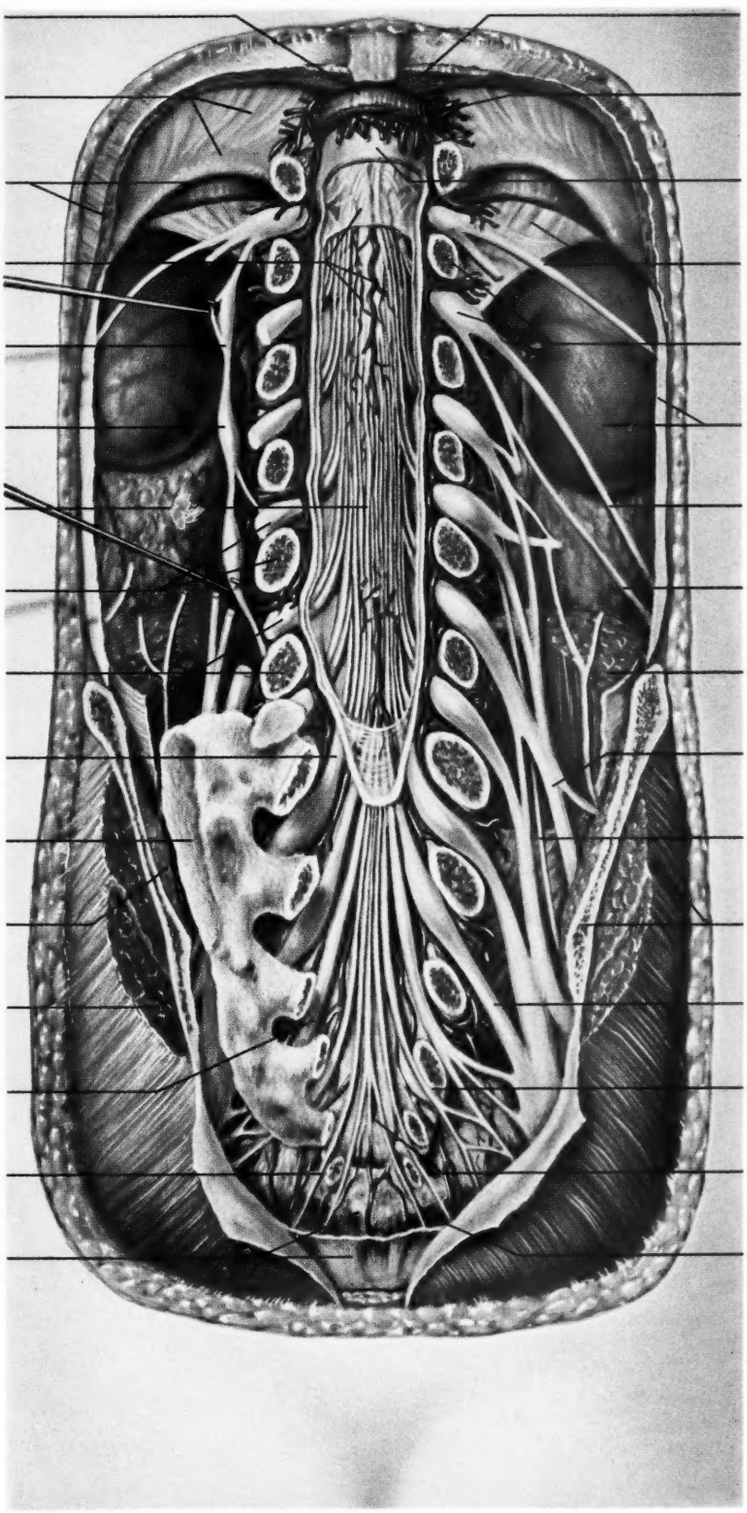
Suspended in a vanishing cream base, COVICONE is easy to apply, is not sticky or greasy. To build up the protective layer, the cream is applied twice daily for 10 days to two weeks. Effective protection can then be maintained indefinitely with a single application every one or two days. COVICONE is indicated wherever skin protection is desired from environmental substances; there are no contraindications except premature application on wet, exudative lesions. At pharmacies in one-ounce tubes and one-pound jars. Abbott

new plasticized cream withstands washing

COVICONE CREAM
TRADE MARK
(Abbott's Protective Skin Cream)

1-151

Lumbar *and* Sacral Regions *of the* Spinal Cord



This is one of a series of paintings for Lederle by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where aureomycin may prove useful.

Lederle

A wide variety of infections of the spine are caused by organisms susceptible to

Aureomycin

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Ascorbic Acid	100 mg.
Thiamine HCl	0.5 mg.
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1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937
2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.
3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

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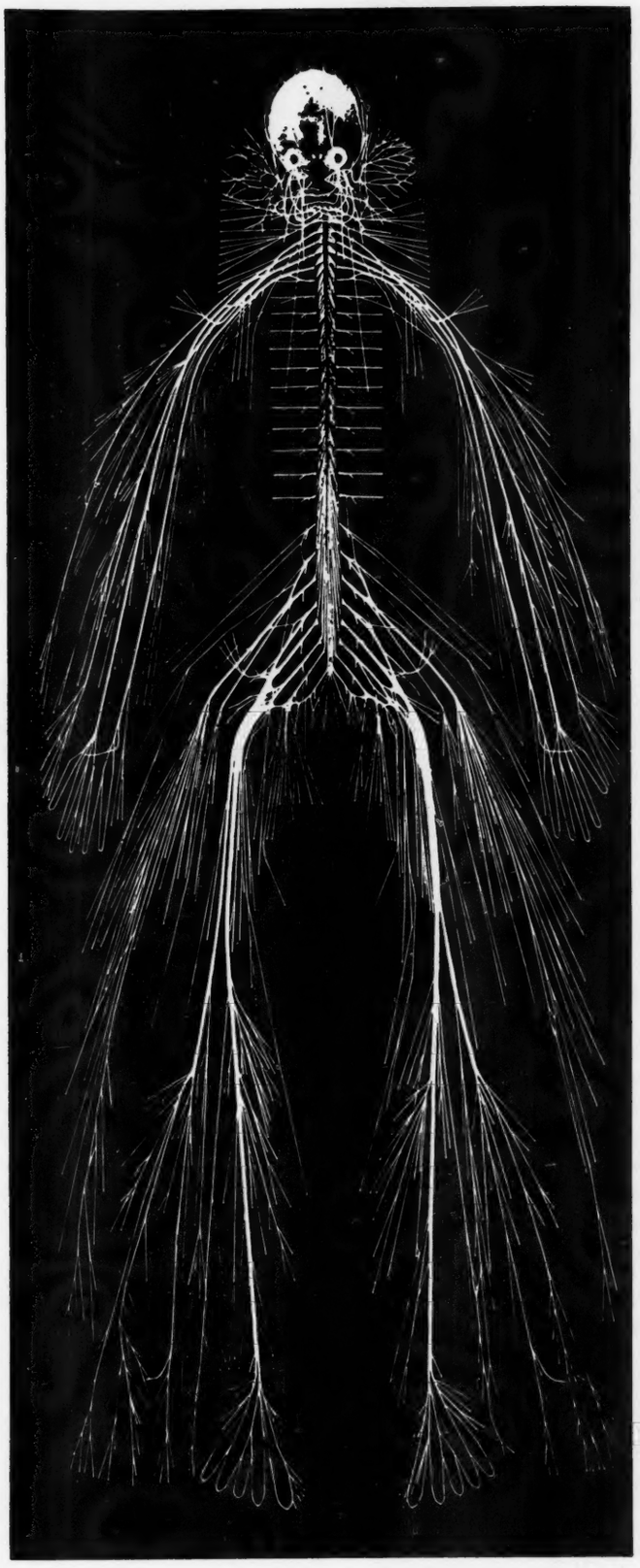

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. . . highly palatable Elixir, and Tablets. Also available, BĒPLETE with BELLADONNA for combined antispasmodic-sedative action; Elixir or Capsule form.

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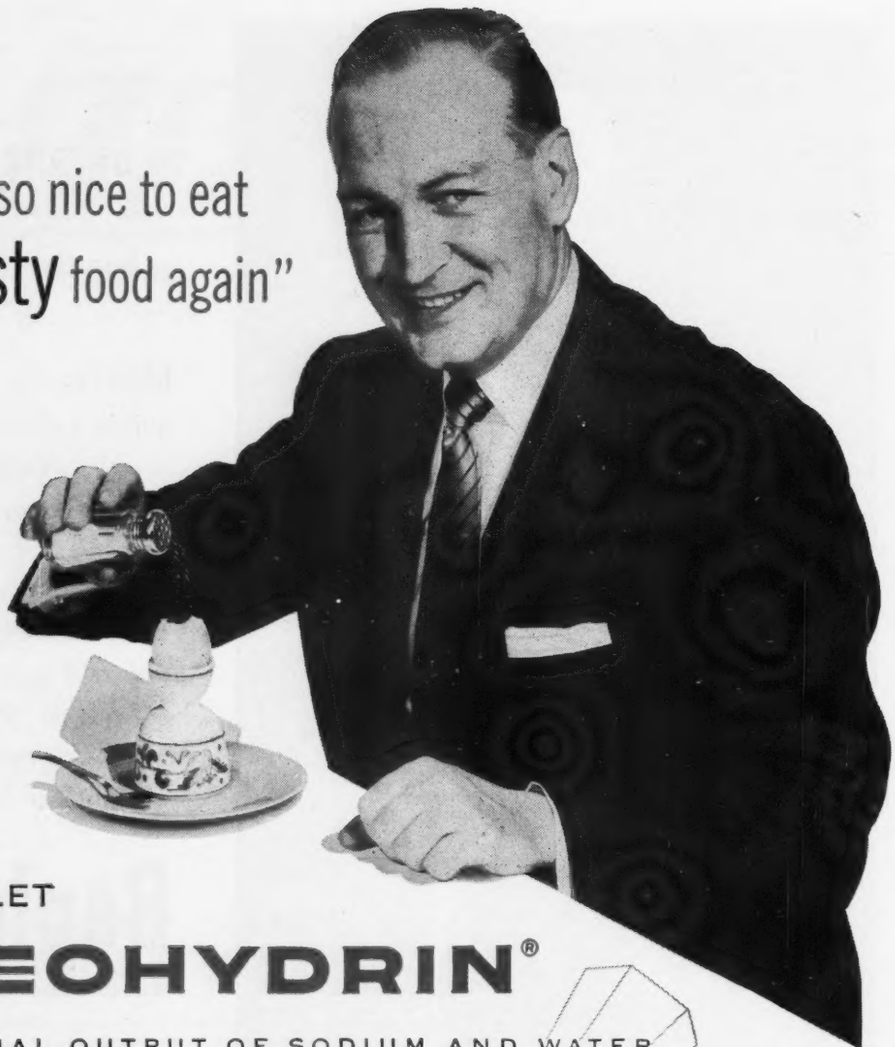
← Dissection of nervous system by R. P. Weaver, A.M., M.D., Sc.D., late Professor of Anatomy, Hahnemnan Medical College and Hospital. Courtesy of Hahnemann Medical College Museum.



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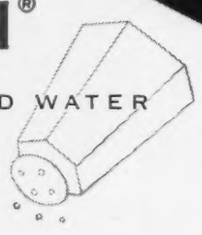

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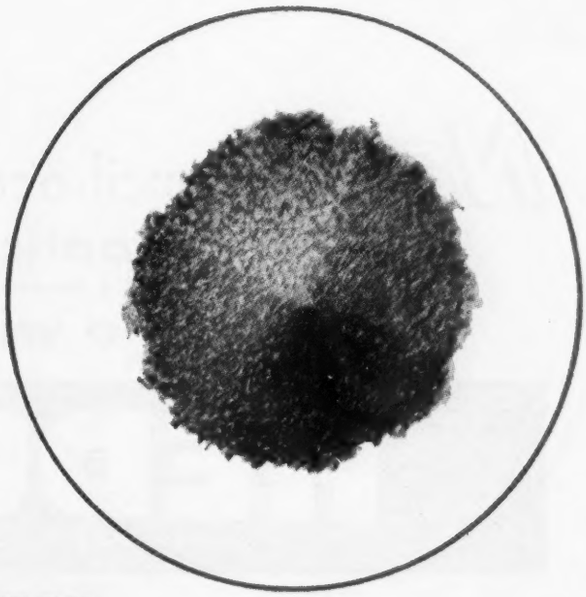

for restoration

and maintenance

of normal bowel function

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BULK-LUBRICANT FOR PHYSIOLOGIC TREATMENT OF CONSTIPATION

SIBLIN provides a granular, water-absorbent derivative of plantago which mixes intimately with food residues to form a soft, gelatinous mass in the large intestine. Nonirritating and virtually unaffected by digestive ferments, this smooth, cohesive mass provides bulk and lubrication for easy passage through the bowel. To aid in improving peristaltic function, SIBLIN contains, in each heaping teaspoonful, approximately 2 mg. of vitamin B_1.

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Dosage: constipation, two teaspoonfuls, morning and night, with a full glass of water.
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supplied: 4-ounce and 16-ounce packages.

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oral anticoagulant
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with a wide range of safety

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Permits dependable prothrombin control with little risk of dangerous fluctuations

- **HEDULIN is not cumulative in effect—provides greater uniformity of action and ease of maintenance**
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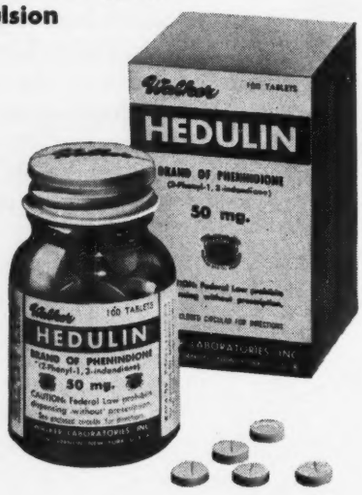

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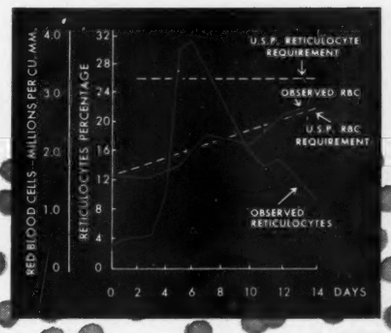

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Crystalline Vitamin B_{12} U.S.P... 6 mcg.
Intrinsic Factor..... 30 mg.
Supplied: Bottles of 30 tablets.

Biopar produces prompt, positive reticulocyte and erythrocyte response in patients with pernicious anemia.

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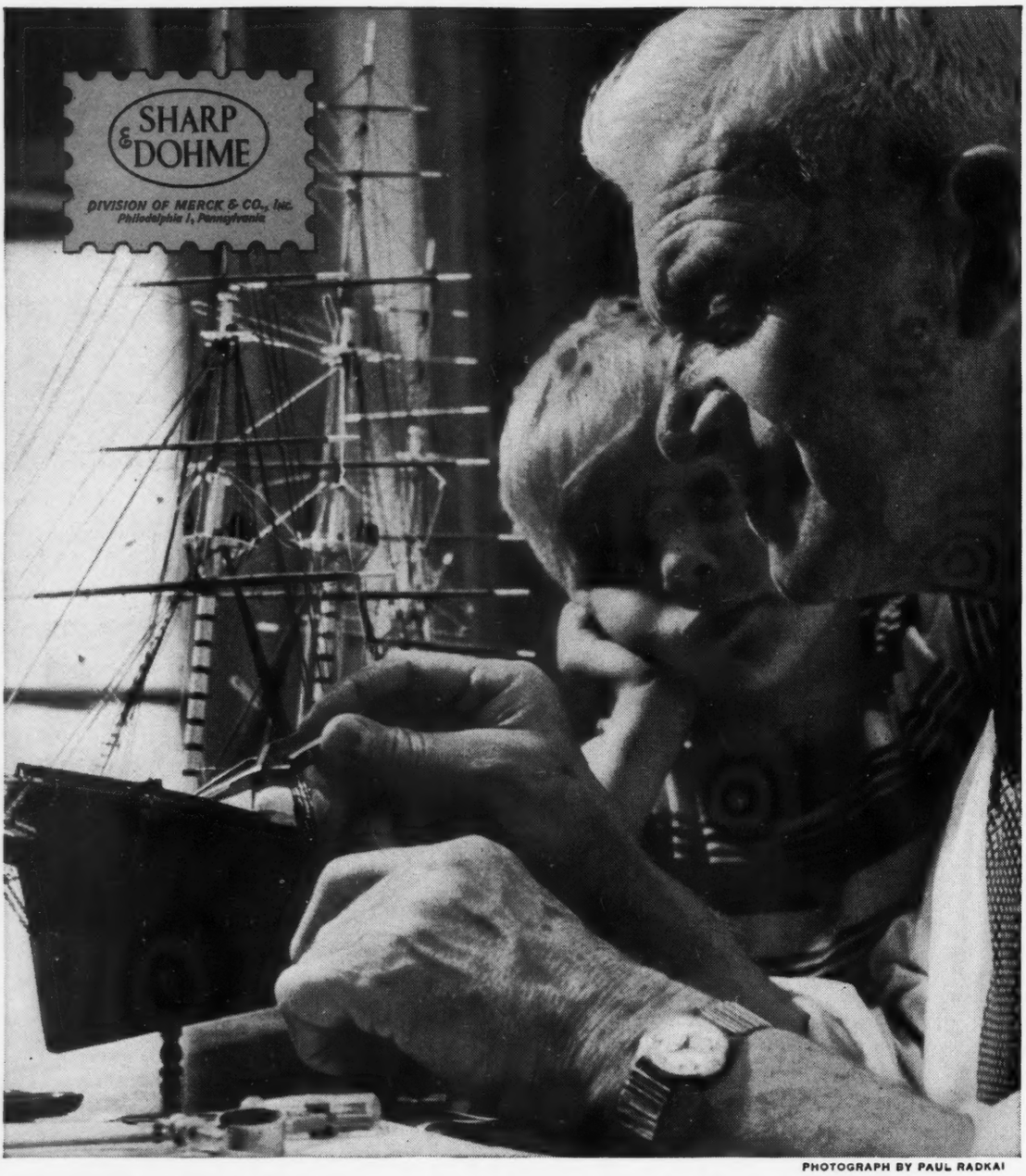

PHOTOGRAPH BY PAUL RADKAI

From 6 to 60... the preferred dosage form

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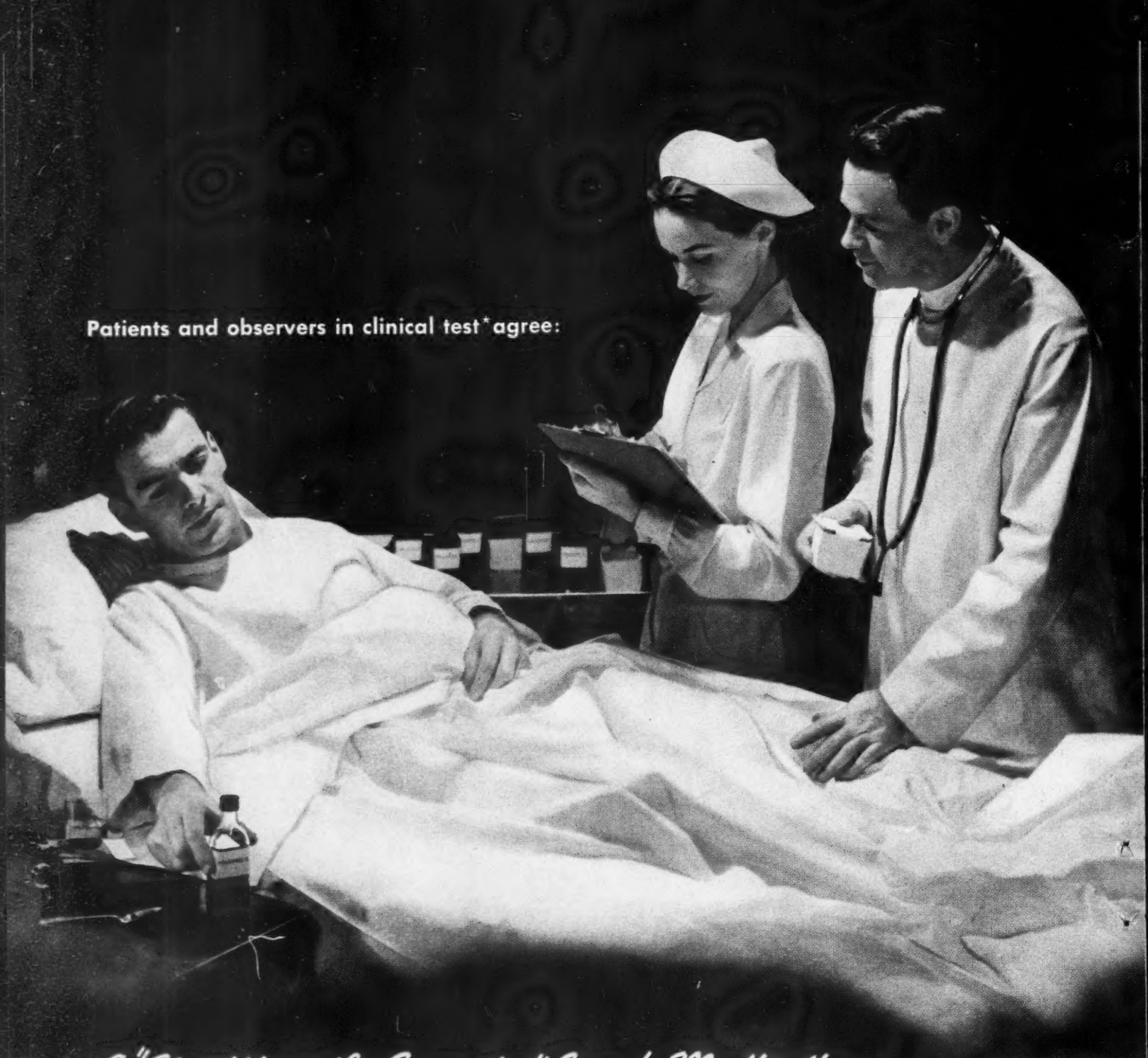

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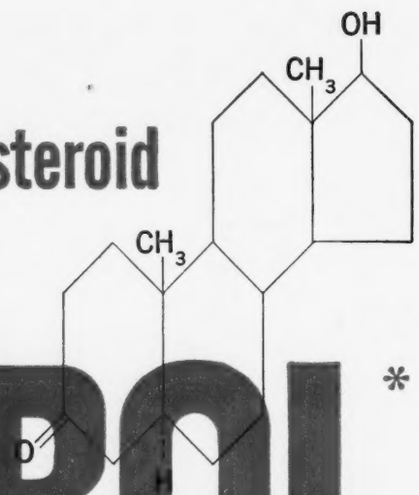

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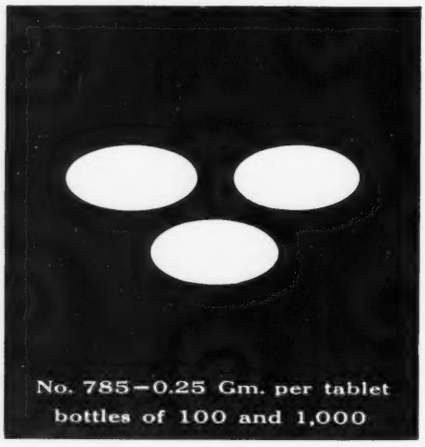

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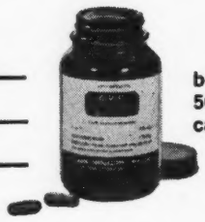

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The American Journal of Medicine

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Editorial

Leptospiral Infections of Man

ONE of the significant developments in the field of infectious disease is increasing recognition of the potentialities of human leptospiral infection. New clinical syndromes have been delineated, and an unsuspected prevalence of this form of infection has been demonstrated.

There are certain obvious reasons for the tardiness in advancement of our knowledge of the leptospiroses. A prominent factor has been the lack of diagnostic procedures suitable for use in clinical laboratories. The organisms can be cultured from blood, urine or spinal fluid but the procedure requires special media and incubation at 25° to 30°C.; even under these conditions growth is slow and can be demonstrated only by examination of the culture with the aid of dark-field microscopy. Recovery of the organisms by animal inoculation is also possible but not feasible for routine clinical practice. Under certain circumstances leptospira can pass through bacterial filters and, as will be pointed out later, this has led to the assumption that infection was caused by ultramicroscopic viruses more than once.

Serology is the means which offers the best hope of being adaptable to routine clinical use. Up to the present time agglutination of living organisms has been the only satisfactory method but this necessitates maintenance of cultures in each laboratory. Progress toward the development of stable antigenic fractions for complement fixation tests, which may be used generally in hospital laboratories, is being made at the U. S. Army Veterinary Medical Division by Yager, Gochenour and associates.

Leptospiral infection is widely disseminated among wild and domestic animals, including rats, mice, dogs, cattle, swine and horses. In some of them the infection is not rapidly fatal but is characterized by a carrier state wherein living organisms are shed in the urine over long periods of time. Human beings may accidentally be infected as a result of contact with material contaminated by such urine, or by handling the flesh of freshly slaughtered animals. There is an occupational hazard, therefore, to certain types of work, including farming, dairying, fish-cutting, slaughter-house work, sewer work and coal mining. Swimming in contaminated pools is another cause of human infection. Cases are most frequently encountered in the summer, possibly because leptospira do not survive long in the cold. The enhancing effect of warm weather may also explain the fact that leptospiral infections appear to be more common in the southern part of the United States. However the disease is in no sense limited to warm areas, since leptospiral infection has been recognized in Massachusetts, Connecticut, New York, Ohio, Michigan, Illinois and Minnesota.

The best known clinical picture of leptospiral infection is Weil's disease, which is characterized by sudden onset with severe muscle pain, repeated chills, high fever, conjunctival injection and hemorrhagic manifestations. There may be meningeal signs, and the spinal fluid usually shows some degree of pleocytosis. At the end of the first week the fever may subside but at this time the most serious manifestations, hepatitis and nephritis, become evident. Mortality is 15 to 30 per cent in icteric cases, the rate being higher in older age groups, death resulting from a combination of the effects of hepatitis and nephritis. Cases of leptospirosis have been recognized in which there is acute nephritis with little or no evidence of hepatitis; these could easily be confused with acute glomerulonephritis.

Recent work by Gochenour and his associates has disclosed that the disease previously known as Fort Bragg, or pretibial, fever is caused by L. autumnalis, a strain not previously known to be present in the United States. An agent, presumed to be a virus, had been recovered from the blood of patients with this disease, and maintained by animal passage for years before

its true identity was demonstrated. The clinical picture is that of a self-limited febrile illness characterized by malaise, headache, enlargement of the spleen and an erythematous eruption principally noted on the anterior aspects of the legs.

European clinicians have recognized since the early 1930's that some individuals with leptospiral infection present the picture of benign aseptic meningitis. This disorder, known in Europe as "swineherd's disease," for some years was thought to be a viral infection closely related to lymphocytic choriomeningitis. The same entity has recently been recognized in the United States, caused by L. icterohemorrhagiae, L. canicola or L. pomona. The illness usually lasts one to three weeks, its features resembling those commonly associated with viral infections of the meninges, such as lymphocytic choriomeningitis, non-paralytic poliomyelitis or mumps meningitis. The cells in the spinal fluid are predominantly mononuclear, the spinal fluid sugar content is normal, and there is no peripheral leukocytosis. Rarely, leptospiral infection of the central nervous system presents evidence of *encephalitis*, with clouding of consciousness and cranial or peripheral nerve palsies.

It is reasonable to assume that many, perhaps most, human leptospiral infections take the form of short self-limited febrile illnesses without distinctive localizing signs, manifested by fever, muscle pain and perhaps respiratory or gastrointestinal symptoms. In various localities these mild forms of illness are known by such names as field-fever, mud fever, cane-cutters' disease, swamp fever and seven-day fever. In this country and abroad infection caused by L. canicola is sometimes designated canicola fever. Actually L. canicola can cause Weil's disease, benign aseptic meningitis or a non-distinctive febrile illness.

A late complication of leptospiral infection is iridocyclitis, which may arise some weeks to several months after an acute systemic infection in one of the forms listed above. The connection between the acute ophthalmic lesion and the preceding illness can easily be overlooked because of the long free interval between them.

It is interesting to note that children seem to be relatively resistant to all recognized forms of leptospiral infection. In adolescence and young adulthood the meningitic forms are likely to be encountered, while the Weil's disease variety is most common in persons past the age of thirty.

A peculiar feature of human leptospiral infection is the difference in leukocyte response depending on the clinical form of the disease. In Weil's disease there is usually a leukocytosis ranging from 12,000 to 25,000. In leptospiral meningitis, on the other hand, the figure is usually in the normal range. No explanation for this rather unique phenomenon is obvious.

Present therapy of the leptospiroses is unsatisfactory. Clinicians abroad have from time to time described beneficial effects from the early administration of antiserum; but the fact that the severest manifestations of Weil's disease may evolve after the natural development of antibodies, makes it seem unlikely that this form of treatment has much to offer. Antibotics have been shown to have a protective action in experimental leptospiral infections, and numerous case reports claiming benefit from penicillin or aureomycin in human leptospiroses have been published. In view of the great variability in the clinical disease from patient to patient, these reports are difficult to evaluate. The only study in which chemotherapy was tried systematically in a sizable number of cases is that of Hall and associates, based on experience in Puerto Rico. The results obtained showed no significant benefit from penicillin, streptomycin, aureomycin, terramycin or chloromycetin, alone or in combinations.

It is safe to predict that henceforth human leptospirosis will be recognized with more frequency in America, and that still further knowledge of the varied clinical forms will be forthcoming.

PAUL B. BEESON, M.D.

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Clinical Studies

Ineffectiveness of Aureomycin in Primary Atypical Pneumonia*

A Controlled Study of 212 Cases

MAJOR STUART H. WALKER, M.C.
Fort Meade, Maryland

SUBSEQUENT to the introduction of aureomycin in the therapy of patients with primary atypical pneumonia it was concluded that this drug exerted a beneficial effect upon the duration of fever and malaise in this disease and upon the incidence of distinct remissions of these manifestations within forty-eight hours of its introduction.[1–12] However, as these conclusions were based upon the insubstantial evidence of uncontrolled or poorly controlled studies, and no effect of this agent could be detected in certain cases,[13] or in certain types of cases,[11] or upon certain manifestations such as cough,[3] some skepticism in regard to this supposed efficacy seems justified. The initial impression that aureomycin was effective in a variety of presumably small-virus diseases was subsequently changed by demonstrations of its ineffectiveness in influenza, herpes zoster, infectious hepatitis, variola, varicella and infectious mononucleosis so that now the only clear evidence of its efficacy in virus infection is in the diseases of the psittacosis-lymphopathia venereum group. These factors and the known variability and usually benign course of primary atypical pneumonia indicated the need for a large-scale controlled reevaluation of the effect of aureomycin, not only upon the duration of fever but upon the quantitative and qualitative aspects of all manifestations of the disease state to determine whether this agent altered the natural course of this disease in any way.

This paper presents the results of such a study in 212 carefully controlled, closely comparable cases of primary atypical pneumonia from a single epidemic. The subjects were mechanically separated into aureomycin and aureomycin-simulated placebo treated groups at the time of hospitalization.

MATERIAL AND METHODS

The material presented herein consists of 212 patients with primary atypical pneumonia admitted to the Infectious Disease Section, William Beaumont Army Hospital, during the course of a moderate epidemic of this disease at Fort Bliss, Texas, during the winter and spring of 1951–1952. The patients were chiefly young soldiers in basic training, although a lesser number of seasoned troops and adult civilian dependents are included. Because of the prevalence of this and other respiratory diseases, available hospital beds were limited and therefore only those patients who were moderately to severely ill were admitted.

All patients in whom a clinical diagnosis of primary atypical pneumonia was made at the time of admission were admitted to the study. Initial diagnosis was based upon the gradually progressive development of fever, malaise, frontal headache, cough and substernal chest pain, with or without the concomitant physical and radiologic findings of alveolar pneumonia. Clinical, serologic, hematologic and epidemiologic evidence has been presented elsewhere which indicates that this disease frequently manifests itself without radiologic evidence of pneumonia.[14] Repeated cultures of sputa and throat flora, peripheral blood counts, cold hemagglutination tests, skin tests with tuberculin and coccidioidin, and radiographic examinations of the chest were performed in all patients to establish the diagnosis further. Cultures of sputa and gastric contents for tubercle bacilli,

* From the Pediatric and Infectious Disease Section, William Beaumont Army Hospital, Fort Bliss, Texas.

blood cultures for pneumococci, serologic tests for Q fever and psittacosis, examinations of stained blood smears for plasmodia and histoplasmin skin tests were performed in selected patients to eliminate these entities from the etiology of the epidemic disease. Thirty-two patients were subsequently eliminated from the study because of the diagnosis of bacterial pneumonia, pulmonary tuberculosis, coccidioidomycosis, streptococcosis, pleurodynia and malaria, or because of our inability to establish any definite diagnosis. Patients with positive tuberculin or coccidioidin skin tests in whom the diagnosis of primary atypical pneumonia could not be corroborated by serologic means were eliminated. A fourfold rise in cold hemagglutination titer was detected between acute and convalescent serum specimens (usually obtained ten days after discharge) in 36.3 per cent of all patients (51.2 per cent of patients with radiologic evidence of pneumonia, 17.1 per cent without).

Patients were divided into two groups; one group was treated with aureomycin, 0.5 gm. every six hours until the temperature was normal for two days or for a minimum of three days, and one group was treated with yellow, aureomycin-simulated placebo capsules in the same capsule dosage and for the same duration. Selection for treatment was based upon the character of the last digit of the hospital register number (which are assigned chronologically to all admissions); odd numbers received placebo, even numbers, aureomycin. No other antibiotic agents were administered. No antipyretics or analgesics were administered except in occasional single doses for the control of extremely high fever or severe cough, headache or chest pain. Gastrointestinal irritation was the only sign of aureomycin toxicity and this occurred in less than 10 per cent of all patients. In a few it was necessary to reduce the dosage to 0.25 gm. every six hours after two days of therapy; in no case was the drug discontinued earlier than intended.

Evaluation of the effects of therapy was accomplished by recording the course of the signs and symptoms of disease on special record forms designed for this purpose. Temperature was obtained orally every four hours until continuously normal for three days. The character and degree of the signs and symptoms were recorded daily on a 1-2-3 scale of severity. Inasmuch as all evaluations were performed by the same observer who was unaware of the therapy being administered, it is believed that a proportional representation of the degree of disease was recorded for each manifestation of each patient. The duration of the various manifestations of disease, as presented in the tables and charts, was computed as the number of calendar days elapsing between (and including) the day of initiation of therapy and the day of last appearance of a distinct evidence of that manifestation designated in the scale as ½. In the case of fever a temperature of 99.6°F. was considered as the last distinct evidence of the manifestation. Symptoms and signs of disease recorded as ¼ and temperatures greater than 98.6°F. were detected for longer periods of time but for the purposes of analysis it was considered that a more comparable time of termination of a manifestation could be obtained as defined. All duration figures are thus less than actual and indicate the course of distinct disease. Inasmuch as no indication of an aureomycin effect upon the course of the radiologic evidence of pneumonia has been detected in previous studies and as it was not possible to retain all patients in the hospital until they were radiologically negative, no attempt was made to evaluate the duration of radiologic pneumonia in the large groups. However, as hospitalization was sufficiently prolonged and chest radiographs were taken regularly at five-day intervals in most instances a comparable evaluation of the duration of radiographic abnormalities from the onset of therapy to the last positive radiograph was possible in the severe cases of each group. In addition, an evaluation of the incidence of progression of the radiologic findings during the course of hospitalization was possible in all patients.

The close comparability of the treated and untreated groups is demonstrated in Tables I and II. As patients were chiefly derived from troops in basic training the average age, sex and race of the groups is almost identical, mainly young, white, adult males. The average duration of disease prior to the introduction of therapy is probably the most significant single factor in evaluation of the effects of such therapy upon the natural course of the disease, and this factor is almost the same for the treated and untreated groups both when radiographically positive patients are considered alone and when all patients are considered together. The severity of the disease as judged by the occurrence of a temperature elevation greater than 102°F. or

the presence of severe symptomatology, grade 3, indicates that the untreated group contained slightly more severe cases than the treated group. Cold hemagglutination was also detected more frequently in the untreated group but this is probably not a good indication of severity.

TABLE I
COMPARABILITY OF THE TREATED AND UNTREATED GROUPS—ALL PATIENTS

	Aureomycin Group	Placebo Group
Number of cases	111	101
Sex—male, percentage	95.5	93.1
Age—years, average	20.6	21.2
Race—white, percentage	96.2	94.4
Duration of disease prior to therapy —average in days	3.8	4.0
Severity		
Fever—greater than 102°F., percentage	66.6	78.2
Symptomatology—grade 3, severe, percentage	29.7	36.6
Rales—presence, percentage	54.0	63.4
Cold hemagglutination—presence, percentage	33.1	42.5
Radiologic evidence of pneumonia —presence, percentage	60.3	50.4
Leukocytosis—greater than 15,000, percentage	17.1	9.9

Despite the slightly greater incidence of distinctly evident moist alveolar rales in the untreated group, a larger percentage of patients demonstrated radiographic pneumonia in the treated group. This discrepancy is, of course, eliminated when the radiographically positive patients are considered alone, and may serve partially to counterbalance the effect of the more severe symptomatology of the untreated group when all patients are considered together. A leukocytosis greater than 15,000 W.B.C./cu. mm. was detected almost twice as often in the treated groups but this probably does not indicate any significantly greater severity. The untreated group, all factors considered, probably contained slightly more severely ill patients, and thus the effect of therapy should be accentuated by the comparison.

RESULTS

The effect of therapy upon the various manifestations of the disease state are presented in Tables III, IV and V and the course of the chief disturbances, fever and cough, are graphically presented in Figures 1 to 4. Emphasis has been placed upon the course and duration of the symptomatology inasmuch as, in this relatively benign disease, this is the problem of most concern to the physician and to the patient. To provide a study comparable to those previously reported, complete evaluation of only those patients with radiologic evidence of pneumonia was accomplished separately. To provide a clearer picture of the effect of aureomycin in those patients most in need of therapeutic assistance and because it has been suspected that aureomycin may be significantly effective only in the severely ill,[11] an evaluation of the effect of this drug as compared to placebo was accomplished in severely ill patients of each group only. (Table V.) As previously indicated the duration of signs and symptomatology, as presented in the tables and charts, is derived from measurement of the number of elapsed calendar days between (and including) the day of initiation of therapy (the day of admission) and the last day on which the sign or symptom was distinctly present (not necessarily the last day on which it appeared to a slight degree). The arithmetic average rather than the median was used in the evaluation as this is more familiar, and it was believed that in so large a

TABLE II
COMPARABILITY OF THE TREATED AND UNTREATED GROUPS—PATIENTS WITH RADIOLOGIC EVIDENCE OF PNEUMONIA ONLY

	Aureomycin Group	Placebo Group
Number of cases	67	51
Sex—male, percentage	96.2	98.2
Age—years, average	21.4	20.3
Race—white, percentage	94.3	93.4
Duration of disease prior to therapy —average in days	4.4	4.5
Severity		
Fever—greater than 102°F. percentage	73.1	76.5
Symptomatology—grade 3, severe, percentage	32.8	49.0
Rales—presence, percentage	71.6	70.6
Cold hemagglutination—presence, percentage	43.7	60.7
Leukocytosis—greater than 15,000, percentage	23.8	11.7

series little distortion would be produced by a few unusual values.

In Table III comparison of the duration of the major symptoms, all of which were present in over 85 per cent of the patients, reveals no significant difference between the duration of

TABLE III
EFFECT OF THERAPY UPON VARIOUS MANIFESTATIONS OF THE DISEASE STATE—ALL PATIENTS

	Aureomycin Group	Placebo Group
Symptomatology subsequent to therapy—average duration in days		
Headache	2.77	2.91
Malaise	4.31	4.61
Cough	5.43	4.55
Chest pain	3.71	4.16
Fever subsequent to therapy—average duration in days	3.15	3.27
Rales subsequent to therapy—average duration in days	4.65	4.62
Progression—incidence, percentage	4.5	2.9
Relapse—incidence, percentage	1.8	1.0
Marked remission—incidence, within 48 hours subsequent to therapy, percentage		
Symptoms	15.1	20.8
Fever	35.7	33.7

headache, chest pain and malaise in the treated group subsequent to therapy and in the untreated group when all patients are considered together. The greater average duration of cough in the aureomycin treated group is demonstrated in Figure 2 to be due to its unusual duration in a small proportion of all cases. The duration of fever was not significantly decreased by the administration of aureomycin as its average was 3.15 days subsequent to the initiation of therapy in all patients of the treated group and 3.27 days in all patients of the untreated group. The average duration of distinctly detectable moist alveolar rales (as distinguished from rhonchi) was almost identical in the two groups. In addition to a quantitative analysis of the duration of various manifestations, an analysis was accomplished of certain qualitative factors upon which aureomycin might exert an effect without altering the total duration of disease. The occurrence of a progression of the disease process, meaning a distinct increase in the majority of the signs and symptoms of the disease process (including fever) subsequent to twenty-four hours of hospitalization, was evaluated but no evidence of a beneficial aureomycin effect is detectable inasmuch as progression, although rare, appeared slightly more often in the treated group.

TABLE IV
EFFECT OF THERAPY UPON VARIOUS MANIFESTATIONS OF THE DISEASE STATE—PATIENTS WITH RADIOLOGIC EVIDENCE OF PNEUMONIA ONLY

	Aureomycin Group	Placebo Group
Symptomatology subsequent to therapy—average duration in days		
Headache	2.91	3.17
Malaise	5.06	5.08
Cough	6.34	6.36
Chest pain	4.56	4.81
Fever subsequent to therapy—average duration in days	3.76	3.63
Rales subsequent to therapy—average duration in days	5.95	5.57
Progression—		
Clinical, incidence, percentage	5.9	3.9
Radiological, incidence, percentage	17.4	17.7
Relapse—incidence, percentage	2.9	0.0
Marked remission—incidence, within 48 hours subsequent to therapy, percentage		
Symptoms	11.9	21.5
Fever	37.3	35.3

Similarly, no effect of aureomycin upon the incidence of relapses of the disease state subsequent to apparently complete cessation of signs and symptoms was detectable.

The chief effect attributed to aureomycin in primary atypical pneumonia has been production of a marked remission of fever as well as in symptomatology within forty-eight hours of the initiation of therapy. Evaluation of the occurrence of such marked remissions as judged by a decrease of 1½ grades in all symptoms or a decrease of 3 degrees Fahrenheit in temperature within forty-eight hours of the initiation of therapy revealed that the administration of aureomycin was, indeed, frequently accompanied by such remissions but that such remissions of fever occurred with equal frequency, and of symptoms even more frequently, in the untreated group.

Table IV demonstrates essentially identical

results of the evaluation of the same quantitative and qualitative factors in those patients with radiologic evidence of pneumonia as in the larger groups described in Table III. However, the slight discrepancies apparent between the average duration of the major symptoms in all patients of the treated and untreated groups are no longer apparent and, if not evident previously, it is now clearly demonstrated that aureomycin has no effect upon the natural course of headache, malaise, cough and chest pain in patients with primary atypical pneumonia. Again the average duration of fever (3.76 days in the treated group and 3.63 days in the untreated) and the average duration of detectable rales (5.95 days in the treated group and 5.57 days in the untreated) reveal no significant differences. Evaluation of the occurrence of the qualitative factors, progression and relapse, again shows a greater incidence of these manifestations in the treated group but they occur so infrequently that little significance can be attached to this demonstration. Evaluation of the incidence of progression of the radiologic evidence of pneumonia to involve new or larger volumes of the pulmonary parenchyma, as demonstrated by radiographs taken at five-day intervals, results in incidence figures undoubtedly less than actual but almost identical for the two groups. Thus although figures for total duration of radiologic evidence of pneumonia are unavailable, the incidence of progression would indicate that aureomycin has no effect upon the course of disease in the pulmonary parenchyma. Evaluation of the incidence of marked remissions within forty-eight hours of the initiation of therapy indicates that in patients with radiologic evidence of pneumonia only, as in all patients, such remissions of symptoms and fever occur with equal or greater frequency in untreated patients.

An evaluation of the effect of therapy in severely ill patients, i.e., patients demonstrating radiologic evidence of pneumonia, fever greater than 102°F., rales and grade 3 symptomatology prior to the institution of therapy, is presented in Table v. The average duration of major symptomatology, fever and rales was slightly greater in the treated group in every instance. In these smaller samples this probably indicates the difficulty of assessing the severity of the disease state by an evaluation on any single occasion rather than a detrimental effect of aureomycin upon the duration of these manifestations. The greater average duration in the treated group was chiefly due to inclusion of a few patients with disease of unusually long duration, as indicated by the greater range of durations shown in the table. The average duration, from onset of therapy to last positive radiograph, of the radiologic evidence of pneumonia in these patients was determined and, although undoubtedly less than the actual duration, was almost identical in the two groups, corroborating the previous evidence of a lack of effect of aureomycin upon the disease in the pulmonary parenchyma. The incidence of the qualitative factors, clinical progression and relapse, again demonstrates their greater frequency in the treated group but, as few patients were involved, the difference is not significant. The incidence of radiologic progression was

TABLE V

EFFECT OF THERAPY UPON VARIOUS MANIFESTATIONS OF THE DISEASE STATE*

	Aureomycin Group	Placebo Group
Number of cases	22	25
Symptomatology subsequent to therapy—average duration in days		
Headache	5.2	4.8
Malaise	9.5	7.0
Cough	11.9	8.3
Chest pain	8.0	7.3
Range—all symptomatology, days	4–32	2–14
Fever subsequent to therapy—average duration in days	6.9	5.3
Range—days	1–20	1–14
Rales subsequent to therapy—average duration in days	9.8	8.4
Range—days	2–22	1–19
Radiologic evidence of pneumonia subsequent to therapy—average duration in days	8.1	8.4
Progression—		
Clinical, incidence, percentage	18.2	8.0
Radiological, incidence, percentage	19.1	19.6
Relapse—incidence, percentage	9.1	0
Marked remission—incidence, within 48 hours subsequent to therapy, percentage		
Symptoms	13.6	28.0
Fever	36.3	32.0

* Patients manifesting radiologic evidence of pneumonia, fever greater than 102°F., grade 3 symptomatology (severe), and rales, only.

almost identical in the two groups of severely ill patients as it was in all patients with radiologic evidence of pneumonia. Marked remissions in symptoms and fever within forty-eight hours subsequent to the invitation of therapy occurred with equal or (in the case of symptoms) greater

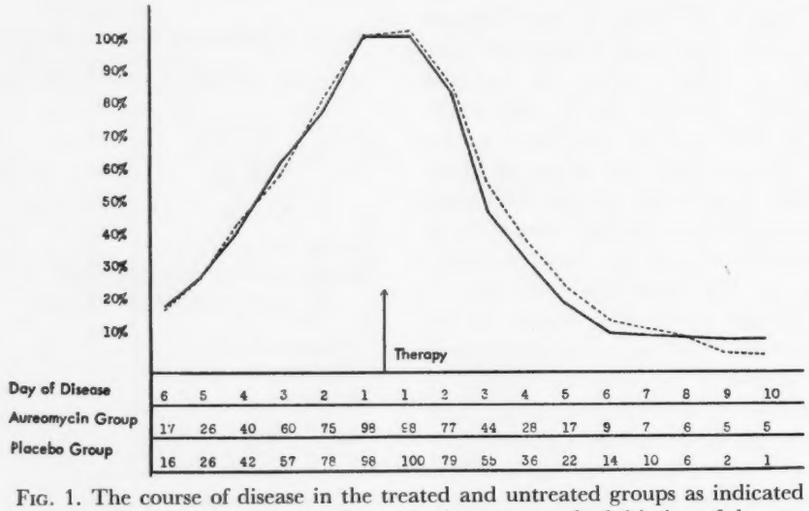


FIG. 1. The course of disease in the treated and untreated groups as indicated by the daily incidence of fever prior and subsequent to the initiation of therapy (all patients).

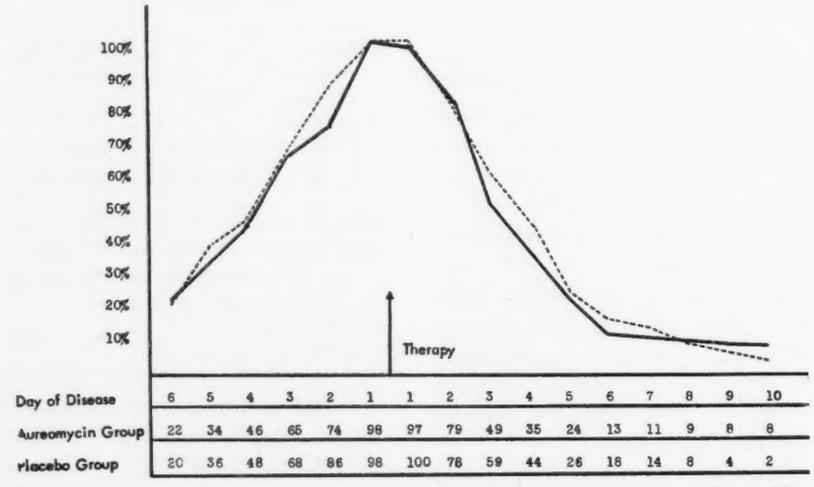


FIG. 2. The course of disease in the treated and untreated groups as indicated by the daily incidence of fever prior and subsequent to the initiation of therapy (patients with radiologic evidence of pneumonia only).

frequency in the untreated group as compared to the treated, indicating a complete lack of effect of aureomycin in qualitatively altering the course of the disease during this period in the severely ill. No indication of any beneficial effect of aureomycin upon any manifestations of the disease in the severely ill is apparent.

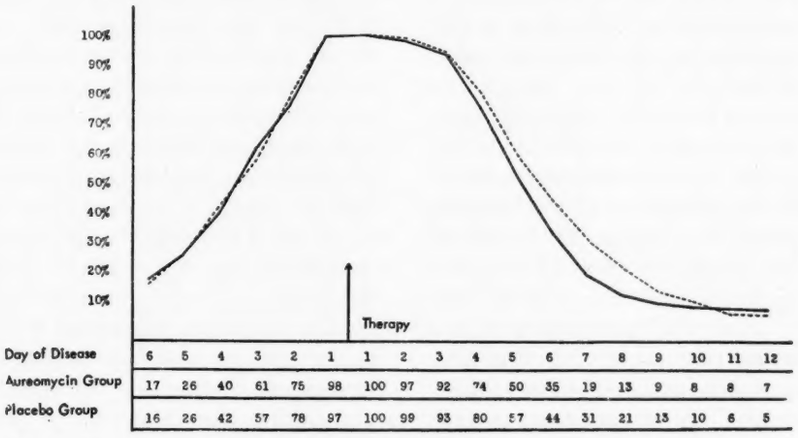
Figures 1 and 2 present the typical course of fever and Figures 3 and 4 the typical course of

the major symptom, cough, in the treated and untreated groups, for all patients and for patients with radiologic evidence of pneumonia only, as indicated by the incidence of the particular manifestation in the group on a particular day prior or subsequent to initiation of therapy. As it is not possible to obtain an accurate indication of the daily incidence of fever during the period prior to the initiation of therapy, the figures for the daily incidence of cough as obtained by history were used in the graphic presentation of the course of both cough and fever. This probably results in a fairly accurate portrayal of the course of prior fever and in any case produces comparable data

for the two groups. The graphs of daily incidence eliminate the difficulties inherent in the presentation of quantitative durations as arithmetic averages and demonstrate the occurrence of certain distorting factors in the groups which account for the occasional slight discrepancies in the arithmetic values. Fever in a greater number of patients of the treated group was of unusually long duration and both fever and cough in the untreated group were more frequently of intermediate duration so that minor differences in the graphic courses of the two groups are apparent at certain points. However, the general course of both fever and cough in all patients and in patients with radiologic evidence of pneumonia only is clearly the same for the aureomycin-treated and untreated groups. These graphs demonstrate that the natural course of the disease, as indicated by comparison with the untreated group, was unaffected by the introduction of aureomycin.

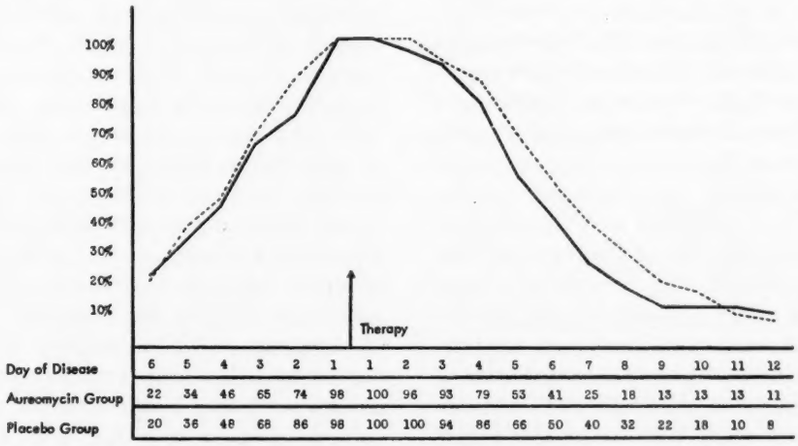
COMMENTS

The early claims that aureomycin was effective in primary atypical pneumonia were based upon the observation of what appeared to be, in comparison with previously observed penicillin or sulfonamide-treated patients, an unusually rapid decrease in fever and malaise, frequently within one or two days after introduction of the new drug.[1–10] Schoenbach et al.[12] carefully compared the total duration of fever and its duration subsequent to hospitalization in a group of thirty-three aureomycin-treated patients with a group of otherwise comparable penicillin and sulfonamide-treated patients ex-



Day of Disease	6	5	4	3	2	1	1	2	3	4	5	6	7	8	9	10	11	12
Aureomycin Group	17	26	40	61	75	98	100	97	92	74	50	35	19	13	9	8	8	7
Placebo Group	16	26	42	57	78	97	100	99	93	80	57	44	31	21	13	10	6	5

FIG. 3. The course of disease in the treated and untreated groups as indicated by the daily incidence of cough prior and subsequent to the initiation of therapy (all patients).



Day of Disease	6	5	4	3	2	1	1	2	3	4	5	6	7	8	9	10	11	12
Aureomycin Group	22	34	46	65	74	98	100	96	93	79	53	41	25	18	13	13	13	11
Placebo Group	20	36	48	68	86	98	100	100	94	86	66	50	40	32	22	18	10	8

FIG. 4. The course of disease in the treated and untreated groups as indicated by the daily incidence of cough prior and subsequent to the initiation of therapy (patients with radiologic evidence of pneumonia only).

tracted from hospital records of previous years. This evaluation demonstrated a statistically significant shorter duration of fever in the aureomycin-treated group. A controlled study comparing the effects of aureomycin and penicillin in partially alternated patients of a group of forty-two cases of primary atypical pneumonia was reported by Meiklejohn and Shragg.[11] This analysis demonstrated no difference in the course of half of the patients of each group but a comparative prolongation of the disease in certain patients of the penicillin-treated group. Because of this, and although relapses occurred in three patients of the aureomycin-treated group, these authors concluded that aureomycin did exert a beneficial effect upon the course of the disease. In 1950 Eaton[15] reported that the administration of aureomycin to cotton rats inoculated with a virus derived from patients with primary atypical pneumonia inhibited the subsequent expected development of pulmonary consolidation. Despite this confirmatory evidence of the efficacy of aureomycin from the biological laboratory, almost every clinical investigator, regardless of his apparent enthusiasm for the drug, detected certain deviations in man which indicated that aureomycin did not exert a general inhibitory effect upon all manifestations of the disease process as was to be expected if it were functioning as an antibiotic agent. No evidence of an effect upon the cough, the outstanding manifestation of the inflammation of the bronchial and bronchiolar walls characteristic of the pathology of this disease, was detected by any investigator, and a distinct lack of effect was sometimes noted.[3] Relapse of the disease state was not uncommonly noted during or after the completion of therapy.[5,10,11] Some severely ill patients demonstrated no response whatever[13] or it was noted that only the severely ill seemed to respond to the drug.[11] Because the effect of aureomycin seemed limited to the inhibition of fever in some studies,[3,5,7,12] it has been considered possible that its action is merely antipyretic. However, no antipyretic action of aureomycin has been otherwise demonstrated. In short, there is no conclusive evidence that aureomycin has any effect in human primary atypical pneumonia; the uncontrolled surmises that it was effective in varying patient groups may be dismissed as such, the partially controlled studies are as significant as the degree of control involved (which were limited), and the apparent failure of any study to demonstrate a general effect of the drug upon the course of symptoms (except fever) or radiologic and physical abnormalities indicates a lack of influence upon the etiological agent itself.

The present study is composed of two entirely comparable groups of patients selected by purely mechanical means during the course of a single epidemic of typical primary atypical pneumonia. Evaluation of the results of aureomycin and placebo therapy was accomplished by the same observer in all instances. He was for the most part unaware of the particular therapy of a given case and the results were not analyzed until the entire series had been completed. The diagnosis of the selected cases seems adequately established by the clinical patterns and the frequency of cold hemagglutination.[16] The possible inclusion of patients with other diseases in the groups without radiologic evidence of pneumonia because of the greater difficulty of establishing the diagnosis of primary atypical pneumonia in such patients is adequately circumvented by the separate evaluation of only those patients demonstrating definite radiologic evidence of pneumonia (still a considerable number—118). Because it has been suggested by at least one previous study[11] that aureomycin exerts a particular effect in patients with prolonged and severe infections, analysis of only those patients who because of initial severity were expected to have prolonged and severe illnesses was also undertaken separately. The comparability of the patients in the latter groups is adequately demonstrated in the tables and in the criteria for admission to the severely ill evaluation. The degree of control, the demonstrated comparability of the various groups and the large number of patients involved indicate that the results of this study should accurately reveal the presence of any influence of aureomycin upon the course of the disease.

To insure that no possible influence would be overlooked, an evaluation of the effects of aureomycin in each of the several groups upon the incidence of the qualitative factors, progression, relapse and remission, as well as upon the quantitative duration of the major symptomatology, fever and the physical and radiologic abnormalities, was accomplished. To eliminate the possibly distorting influence of unusual values in the use of arithmetic averages (which, when differences appeared, chiefly indicated a

greater efficacy of placebo therapy), graphic representation of the daily incidence of fever and cough for the total course of disease was presented for all patients and for patients with radiologic evidence of pneumonia only. From this multiple analysis of the course of primary atypical pneumonia in completely controlled treated and untreated groups it may be justifiably concluded that aureomycin has no influence upon the course of this disease.

The apparent discrepancy between the conclusion of this study and those of previous investigators would appear to be consequent to two major factors: the lack of comparable control patients in the previous studies, which because of the marked variability between epidemics and in individual patients with primary atypical pneumonia, renders such studies invalid, and the frequency of essentially spontaneous remissions in this disease. The results of the present study indicate that it is distinctly unusual for progression of a majority of the signs and symptoms of disease to occur subsequent to hospitalization, and that in one-third of untreated patients a marked remission of fever will occur within forty-eight hours of hospitalization. These data probably indicate the efficacy of bed rest in the treatment of this disease but even more clearly demonstrate how readily a therapeutic agent might be credited with specific efficacy in an uncontrolled study.

The single disturbing factor in the analysis of the effect of aureomycin in primary atypical pneumonia is the well controlled demonstration by Eaton[15] that this drug influences the production of pulmonary consolidation in cotton rats inoculated with a virus derived from patients with this disease and inhibits the survival of the virus in chick embryos. Correlation of this demonstration with the present study indicates that two different viruses may be involved, or that the disease in animals responds differently to aureomycin, or that introduction of the drug very early in the course of the disease is necessary to influence it. Although the latter is quite possible, inasmuch as the drug was successfully introduced in animals during what would be the incubation period of the disease in man, it seems unlikely that some effect would not be detected in human disease were the viruses the same.

SUMMARY

A controlled study of 212 patients from a single epidemic of primary atypical pneumonia is presented in which the effects of aureomycin were compared with the effects of aureomycin simulated placebos in severely ill patients, patients with radiologic evidence of pneumonia only, and in all patients of the series.

Evaluation of the duration of the major symptom, fever, of the physical and radiologic signs of disease, and of the incidence of progression, relapse and marked remission within forty-eight hours of the initiation of therapy indicated that aureomycin does not influence the course of this disease.

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The Treatment of North American Blastomycosis with 2-Hydroxystilbamidine*

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FUNGAL diseases are being diagnosed with increasing frequency in all branches of medicine. This is probably the result of improved and more easily available bacteriologic facilities together with an increased awareness of the existence of these infections. It would seem likely, moreover, that the control and virtual eradication of many more common infectious diseases has tended to focus attention upon the more resistant mycoses.

One of the most serious mycotic diseases is systemic North American blastomycosis. While the incidence of this condition is uncertain, it is not rare. In 1939 Martin and Smith found 347 proven and presumptive cases reported in the literature.[1] During the ten-year period preceding June 1, 1951, sixteen cases of blastomycosis were observed in the John Gaston Hospital and the University of Tennessee College of Medicine. Of this group five were cutaneous and eleven were of the systemic type. In the fifteen months following June 1, 1951, three additional cases were diagnosed at the John Gaston Hospital while another four came to necropsy unrecognized. The etiology in the latter instances was established only by bacteriologic and histologic studies; gross findings at autopsy were not conclusive and clinically these patients had been thought to have tuberculosis or bronchogenic carcinoma. In addition, during this period one of the authors observed three cases of the systemic form of this disease in two other hospitals in the Memphis area. Although the cutaneous type of blastomycosis accounted for only six of the nineteen cases treated at the John Gaston Hospital, it is generally believed that this is the more common form of the disease. This apparent discrepancy can probably be explained by the fact that patients with systemic involvement are gravely ill and therefore much more likely to seek hospitalization.

The clinical features and diagnosis of both cutaneous and systemic North American blastomycosis were discussed in a previous paper.[2] Iodides and roentgen therapy, together with appropriate surgical procedures, yield at least temporary remissions in the majority of instances of cutaneous blastomycosis.[1–9] However, many cases are resistant and exacerbations are common. Treatment of the systemic form of the disease has remained quite unsatisfactory.[7,10] Benham states that disseminated blastomycosis progresses slowly until death ensues.[3] Martin and Smith report a 92 per cent mortality in cases followed two years or longer.[1]

Potassium iodide has been used more extensively than any other drug in the treatment of these diseases; its effectiveness, however, remains uncertain. Martin and Smith believe that it is curative in some cases.[11] However, these investigators reported that iodides are actually harmful when administered to a patient who is allergic to the fungus. They believe, therefore, that all patients with either the cutaneous or the systemic form of the disease should be skin tested and if found to be hypersensitive should be gradually desensitized prior to the administration of iodides. Hyde and Ricketts are of the opinion that iodides are of no value in the visceral form of this disease.[12] Roentgen therapy and innumerable other agents have been employed in the treatment of disseminated blastomycosis with no evidence of sustained improvement.[1,3,13–15] Recently developed chemotherapeutic preparations such as the sulfonamides, penicillin and streptomycin have been demonstrated to be of little value.[16–21] In a previous publication it was reported that

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aureomycin is capable of controlling systemic blastomycosis for a prolonged period of time—perhaps permanently. However, it was not possible to eradicate the causative organism in the tissues; and discontinuance of this antibiotic repeatedly resulted in exacerbation of the disease.[2]

While searching for an effective and non-toxic therapeutic agent for use in blastomycosis, 2-hydroxystilbamidine was considered. In 1945 Elson reported that propamidine—closely related to stilbamidine—is effective *in vitro* against Blastomyces dermatitidis, the causative agent of North American blastomycosis.[22] Following these studies Colbert and his associates described a favorable effect by propamidine when applied topically to the cutaneous lesions of blastomycosis.[23] Subsequently, Schoenbach and his colleagues investigated the clinical action of stilbamidine and propamidine administered parenterally in four cases of systemic blastomycosis.[24–26] They concluded that beneficial results were obtained in three patients and encouraging results in a fourth. Unfortunately, the toxicity of stilbamidine necessitated brief and intermittent courses of therapy. Even so, trigeminal neuralgia developed in three of these cases and it was necessary to discontinue treatment in one instance, although B. dermatitidis could still be demonstrated in the tissue. Other clinicians have confirmed the favorable influence of stilbamidine on the course of cutaneous and visceral blastomycosis. Heilman recently reported that the pulmonary infection in mice which occurs following the intravenous injection of B. dermatitidis is suppressed by stilbamidine injections.[27] Cerebral blastomycosis, which also develops in these experimental animals, was not, however, controlled by this drug.

Stilbamidine administration is complicated by several toxic side actions. Solutions of this substance are very sensitive to light.[28–33] Exposure to sunlight for only thirty minutes results in a definite reduction of therapeutic effectiveness; exposure for two days causes a six-fold increase in toxicity. Animal experiments have indicated that stilbamidine may cause fatty metamorphosis of the liver and degeneration of the convoluted tubules of the kidney.[34,35] Although such effects have not been observed in patients with normal liver and kidney function, Snapper reported that stilbamidine caused exacerbation of renal damage and rapidly progressive uremia in cases of multiple myeloma with kidney involvement.[36] In addition, this agent has an affinity for the peripheral nervous system resulting in a neuropathy which usually involves the face.[37] In the tropics, arms and trunks are also often affected. Collard and Hargreaves reported this type of neuropathy in twenty-two of twenty-four patients who received stilbamidine.[38] Similar effects have been noted by many others.[39–41] Because of these toxic effects, which may be produced by relatively small quantities of the drug, stilbamidine is no longer employed in the treatment of kala-azar.

In an attempt to obtain a non-toxic stilbamidine derivative Snapper investigated 2-hydroxystilbamidine and found that it did not produce trigeminal neuropathy.[42] Furthermore, solutions of this substance were found to be more stable than solutions of stilbamidine. *In vitro* studies disclosed that stilbamidine and 2-hydroxystilbamidine exerted a comparable effect on the mold-like form of B. dermatitidis, although stilbamidine was thought possibly to be more active against the yeast form.[45] As a result of these promising studies it was decided to investigate the action of 2-hydroxystilbamidine* in blastomycosis. Three cases of systemic North American blastomycosis and one case of the cutaneous form of the disease have been treated with this agent.

CASE REPORTS

CASE 1. A forty year old Negro man (S. B.) was admitted to the Medical Service of John Gaston Hospital on April 4, 1952, with the established diagnosis of systemic North American blastomycosis. The history and clinical course of this case through October 19, 1951, were previously reported and will therefore be merely summarized.[2]

The cutaneous stage of the disease in this case began in 1943 when the patient presented himself with ulcerating papulopustular lesions involving the entire face. The diagnosis was readily confirmed by the demonstration of B. dermatitidis. Extensive clinical and roentgenologic studies at this time failed to reveal any evidence of visceral involvement. Treatment during the ensuing four and a half years consisted of potassium iodide and repeated courses of roentgen therapy.

* The 2-hydroxystilbamidine di-isethionate was supplied through the courtesy of the Medical Research Department of the William S. Merrell Company, Cincinnati, Ohio.

The first evidence of visceral involvement appeared in 1948 when finely granular pulmonary infiltrations were noted, with associated symptoms of cough and expectoration, chest pain, dyspnea, fever, night sweats, malaise, weakness and tender enlargement of cervical lymph nodes. In December, 1949, the patient was re-admitted for a twenty-two-month period of hospitalization and treatment with aureomycin (the subject of the previous report).[2] On therapy of 3 to 4 gm. daily of this antibiotic (in total dosage of approximately 2,000 gm.), there was marked improvement of the disfiguring facial lesions. The suppurative cervical lymphadenitis completely subsided; the miliary pulmonary infiltrations completely resolved; and the patient was rendered free of symptoms. Furthermore, while B. dermatitidis had been repeatedly demonstrated in sputum, bronchial secretion and gastric washings prior to aureomycin therapy, all bacteriologic studies became persistently negative. It was evident that aureomycin continuously administered could control the systemic infection.

Less satisfactory, however, was the incomplete healing of the facial lesions in which small numbers of B. dermatitidis could still be demonstrated in biopsied tissue. Moreover, discontinuance of aureomycin was on each of three occasions followed within four to six weeks by clinical, roentgenologic and bacteriologic exacerbations.

Therefore, on September 6, 1951, the patient was rehospitalized; aureomycin and all supportive medication were discontinued and the patient was observed for evidence of reactivation of his disease. One week later (September 13, 1951) the Ophthalmology Service attempted plastic repair of both eyelids; this was unsuccessful. On October 13, 1951, (thirty-seven days after the discontinuance of aureomycin) a papular lesion was observed on the left thigh; biopsy and culture of this tissue revealed B. dermatitidis. However, the chest roentgenogram continued to show no evidence of infiltration. At this time the facial lesion exhibited definite evidence of extension with associated pain and burning. Therefore, on October 22nd, after another chest film was reported as being within normal limits, cortisone therapy was begun. During the first twenty-four hours 300 mg. were administered intramuscularly and thereafter 200 mg. were injected daily. Five days later, October 27th, the skin lesions were much more extensive although discomfort was greatly reduced. (Fig. 1A.) Five prominent areas of activity had developed under cortisone —three over the forehead and one on each ear. Even the recent leg lesion appeared to be spreading more rapidly. Also, a chest roentgenogram on October 27th (after only five days of cortisone) disclosed granular lesions in the first, second and third interspaces on the left. Cortisone was discontinued. Sputum and gastric washing specimens on October 29, 30 and 31 yielded B. dermatitidis on culture.

On November 5, 1951, 2-hydroxystilbamidine* treatment was begun. Initial dosage consisted of 0.11 gm. administered intravenously in 20 cc. of 5 per cent glucose over a period of twenty minutes every other day on four occasions; then, as no toxic effects were noted, this dosage was given daily for ten days. Thereafter medication was further increased to 0.225 gm. every twenty-four hours. There was dramatic objective improvement of the cutaneous lesions. The site of the leg biopsy obtained on November 5th (Figs. 2A and B) had essentially healed by November 11th; no pruritus or burning of the facial lesions was noted after two weeks of treatment. By December 17, 1951, the leg lesion had largely disappeared and a repeat biopsy on this date disclosed reduction in the inflammatory reaction. Of interest was the pathologist's opinion that the few organisms demonstrated in the tissue appeared abnormal —seemed to be degenerating. A culture of this tissue failed to yield B. dermatitidis.

Perhaps the most striking development was the improvement in the patient's mental status. He stated that for the first time in years he believed himself to have a future; he became a great aid to the nurses on the ward and spent long periods at the mirror admiring his face. The eyelids improved in a striking manner with concomitant increase in vision. Serial chest roentgenograms revealed the first indication of clearing on November 23, 1951; but it was not until January 25, 1952, that no evidence of infiltration could be detected. Although medication was discontinued on January 8th the patient continued to improve and by March 3, 1952, only one small area on the forehead appeared to be suspicious of activity. This area

* In this article the term 2-hydroxystilbamidine is used instead of 2-hydroxystilbamidine di-isethionate which was actually injected. The latter compound contains only 54 per cent 2-hydroxystilbamidine.

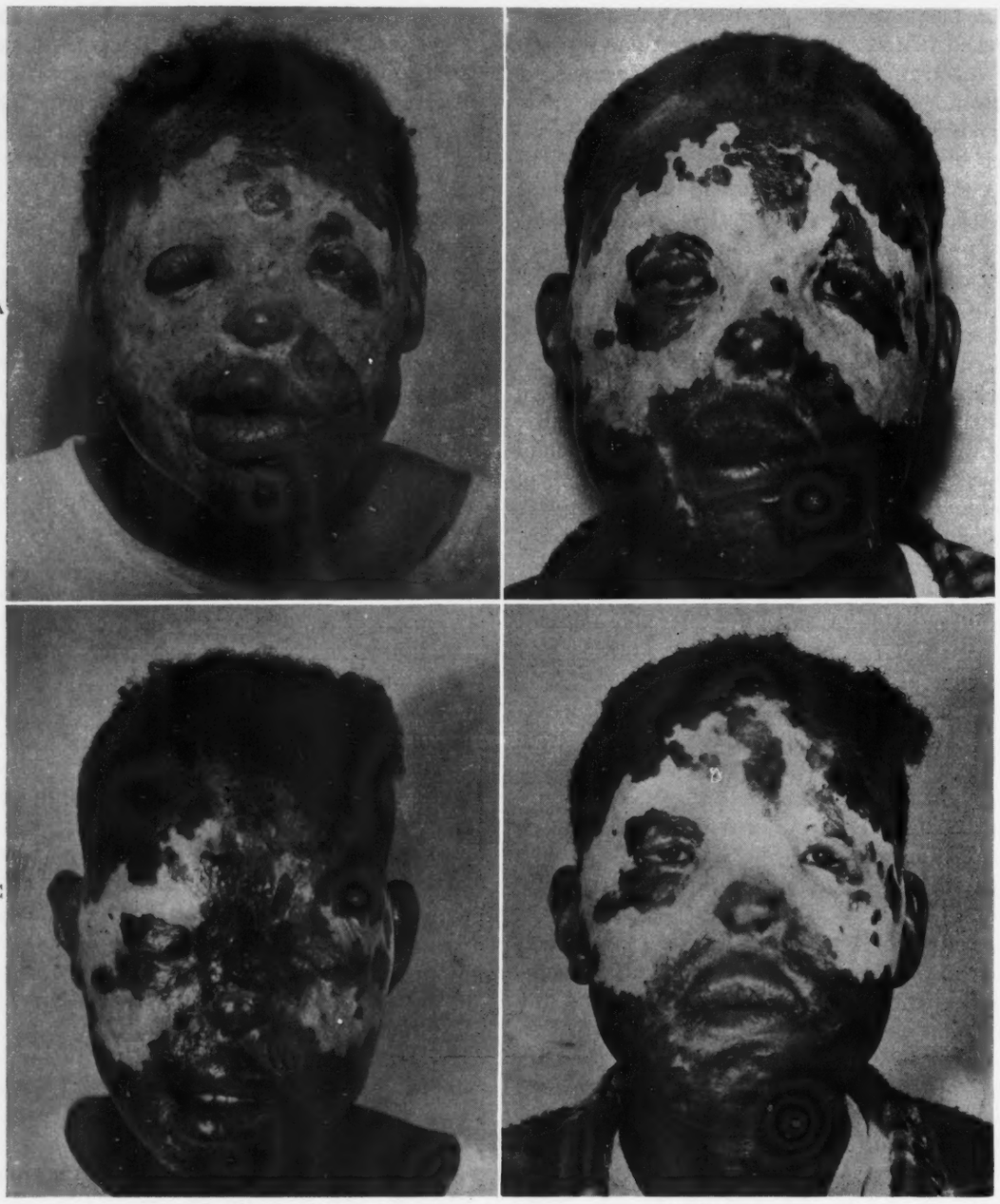
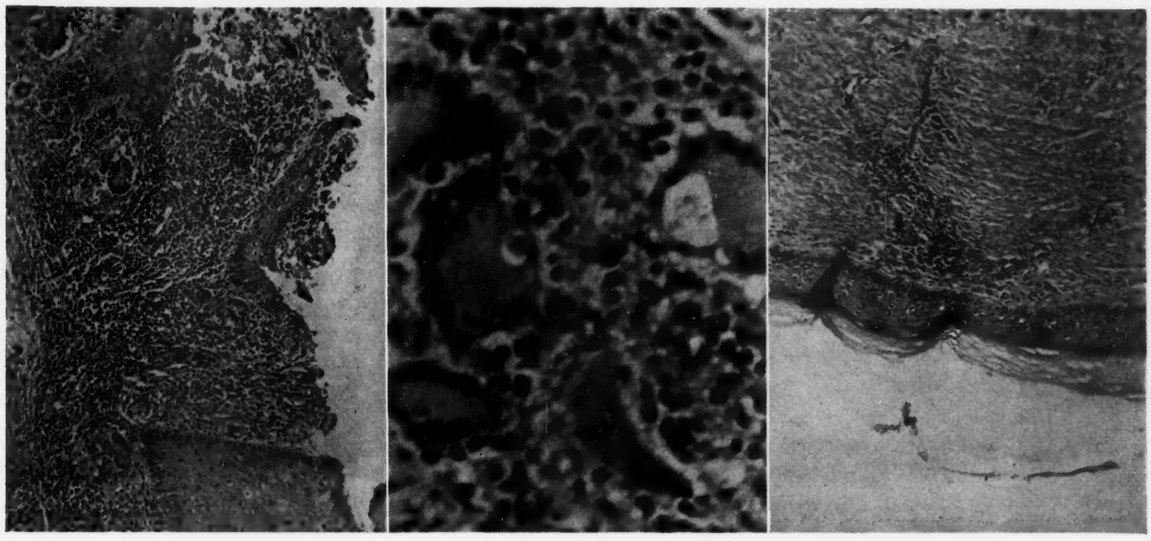


FIG. 1. Case 1. A, facial lesions following cortisone therapy and immediately prior to the initial course of 2-hydroxystilbamidine. B, marked improvement following the first administration of 2-hydroxystilbamidine. C, exacerbation of facial lesions eight and one-half months after treatment. D, rapid response to 4.15 gm. of 2-hydroxystilbamidine, six weeks later.

measured 0.6 by 0.4 cm. (Fig. 1B.) All other cutaneous lesions including the leg ulcer had healed. On that date a biopsy was obtained from the questionable area of facial involvement and also from the leg. (Fig. 2C.) No organisms were detected on microscopic examination by competent pathologists, even with the use of special staining technics. However, a culture of the tissue was subsequently positive. Inasmuch as the chest films had remained persistently clear and four sputum and gastric washing specimens as well as a marrow preparation were negative for fungi, the patient was discharged from the hospital to be observed through the Antibiotic Clinic.

Since no information was available concerning



2A 2B 2C

FIG. 2. Case 1. A, microscopic section of granulomatous leg lesion with giant cells and micro-abscesses; magnification × 90. B, yeast form of B. dermatitidis present in giant cells. C, same lesion four months after initiation of 2-hydroxystilbamidine; lesion practically healed.

the toxicity of such prolonged and massive 2-hydroxystilbamidine treatment, extensive laboratory examinations were carried out during this period of hospitalization. These were primarily concerned with hematologic, hepatic and renal functions and included the following: daily urinalysis, complete blood count and differential white cell study every three days, hematocrit every three days, blood non-protein nitrogen and blood urea nitrogen determinations every three days, hepatic function studies weekly for the first month and then every two weeks (cephalin-cholesterol flocculation, serum bilirubin, total and fractional plasma protein, prothrombin time, alkaline phosphatase and plasma cholesterol) and an electrocardiogram each week. A sternal marrow was obtained before and following treatment as was a determination of the bromsulfalein retention (5 mg. per kg. of body weight at forty-five minutes). No evidence of toxicity was noted.

While the general condition of the patient continued to be excellent there was gradual extension of the involved area on the forehead so that by April 4th it had increased from 0.6 by 0.4 cm. to 1.1 by 0.9 cm. The patient therefore was re-admitted to the hospital for additional 2-hydroxystilbamidine treatment. Unfortunately, due to a limited supply the total quantity of medication administered during this period was only 2.25 gm. Again the lesion improved rapidly and within a month was even smaller than at the termination of previous hospitalization (0.6 by 0.1 cm.). During this period in the hospital no evidence of systemic disease was observed—the chest remained clear and repeated specimens of sputum[8] and gastric washings[3] were negative for fungi. The patient was once more discharged from the hospital.

From May 4, 1952 to September 22, 1952, he was observed at semi-monthly intervals in the Antibiotic Clinic. No medication was administered and no evidence of reactivation of the disease was noted until September 1, 1952. On that date the lesion on the forehead had increased in size and a small papule had developed just below the angle of the left jaw. Within three weeks there was rapid extension. The nose became involved, new lesions appeared on both ears and the eyelids became markedly edematous. (Fig. 1C.) However, the chest roentgenogram remained clear and three gastric washings failed to reveal B. dermatitidis. Treatment with 2-hydroxystilbamidine was reinstituted on September 25, 1952, using 0.225 gm. in 20 cc. of 5 per cent glucose in distilled water intravenously each day until a total of 4.15 gm. of the drug had been given. Because of a limited supply therapy was somewhat intermittent. Again, rapid objective and subjective improvement occurred. By November 13th only two small areas suggestive of activity remained, one on each ear. (Fig. 1D.) The new lesion beneath the left angle of the jaw had virtually disap-

peared. There was still no evidence of systemic disease.

A series of complete fixation tests* performed in this case was of interest: *February 28, 1952:* A reaction of doubtful significance was obtained with both the yeast-like cell antigen and the extract antigen of the yeast-like cells of Histoplasma capsulatum. There was evidence of a strong reaction with the yeast-like cell antigen and the extract antigen of the yeast-like cells of B. dermatitidis. The exact titer with these antigens could not be determined since the reactions were not entirely typical. *April 18, 1952:* A reaction titer, 29, was obtained in the complement fixation test with the extract antigen of the yeast-like cells of B. dermatitidis and evidence of a reaction was obtained with the yeast-like cell antigen. This reaction, however, was not entirely typical and therefore the exact titer could not be determined. *October 27 and November 19, 1952:* Evidence of reactions were obtained in the complement fixation tests with both the yeast-like cell antigen and the extract antigen of the yeast-like cells of B. dermatitidis. Inasmuch as the results were atypical the exact degree of the reaction could not be determined.

Comment. This chronic case of systemic North American blastomycosis had for nine years resisted many different therapeutic trials. It appears that 2-hydroxystilbamidine was effective against both the cutaneous and systemic lesions of blastomycosis. *In vitro* studies established a definite inhibitory effect by this diamidine. (Table 1.) Inasmuch as this patient received prolonged and extensive treatment (19.6 gm. to date) comprehensive laboratory studies were combined with careful clinical examinations to determine any evidence of toxicity. No such evidence was noted. Likewise, there were no subjective symptoms of toxic effects. The action of cortisone in this case is of interest and suggests that, as in tuberculosis, it may be contraindicated in blastomycosis. It would appear that if sufficient 2-hydroxystilbamidine can be obtained this patient's disease can at last be eradicated.

CASE II. A four year old Negro girl (T. H.) entered John Gaston Hospital on April 17, 1952, because of multiple chronic skin lesions, cough, fever and weight loss. Upon admission to the hospital the child was in a semi-stuporous condition.

Seven months prior to hospitalization a small, painless papule was noted on the dorsum of the left wrist. It was believed by the parents that the child had fallen and injured her wrist—perhaps had introduced a splinter of wood into the skin. A private physician incised the lesion, with the subsequent development of a chronic draining sinus. During the ensuing six months multiple additional lesions developed involving the scalp, face, neck, thorax, scapulae, abdomen, hips and all extremities. For three weeks prior to admission to the hospital the right labium and right lower extremity had been swollen and tender. Pyrexia had been present for at least five and a half months; this apparently had been low grade in type and had not been associated with frank chills. During the course of the patient's illness she had received several courses of penicillin and sulfadiazine.

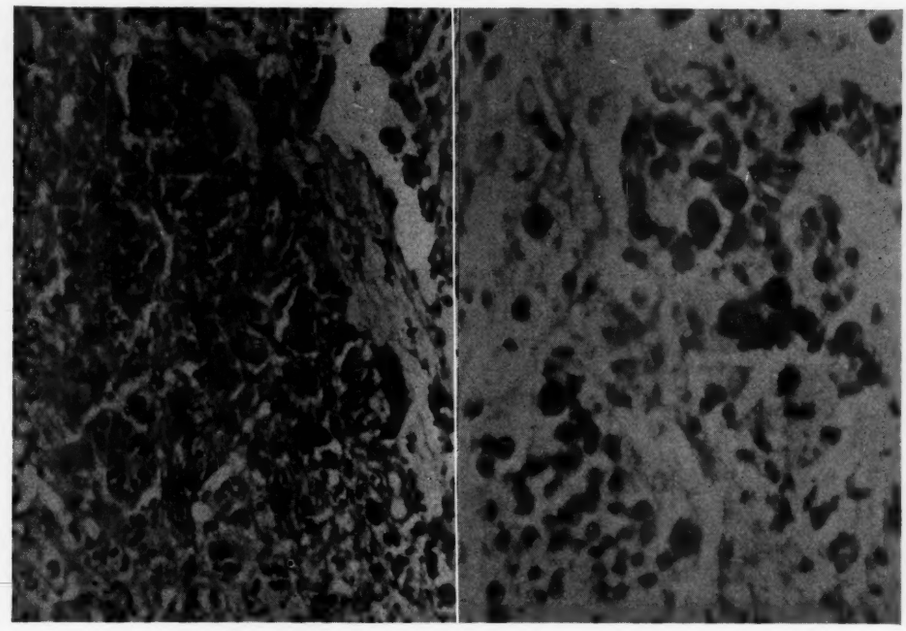
The past history was non-revealing. A review

TABLE 1

COMPARISON OF THE SENSITIVITY OF B. DERMATITIDIS TO STILBAMIDINE AND 2-HYDROXYSTILBAMIDINE—N. Y. STRAIN

μg. 2-OH Stilbamidine/cc.	μg. Stilbamidine/cc.	Weeks after Inoculation			
		1	2	3	4
Mycelial Phase					
0.5	0	+	++	++	++
0	0.5	+	++	++	++
1	0	±	++	++	++
0	1	±	±	+	++
3	0	−	±	+	++
0	3	−	−	−	−
5	0	−	−	−	±
0	5	−	−	−	−
Yeast Phase					
0.5	0	++		++	
0	0.5	−		++	
1	0	−		++	
0	1	−		±	
2	0	−		+	
0	2	−		−	
3	0	−		−	
0	3	−		−	

* The complement fixation determinations reported in this paper were obtained through the cooperation of Dr. Elizabeth L. Hazen of the Branch Laboratory of the Division of Laboratories and Research of the New York State Department of Health.



3A 3B

FIG. 3. Case II. A, biopsy of skin lesion before initiation of 2-hydroxystilbamidine treatment. Cellular infiltration with many giant cells is present; magnification × 190. B, same lesion using magnification × 450 which reveals many yeast forms of B. dermatitidis.

of the child's environment disclosed that she played out of doors the major portion of each day and had two pet dogs. The latter were said not to have had any illness or skin lesions.

Examination on hospitalization disclosed that the temperature was 39.3°C. (rectal), pulse 160 and respirations 28. The patient appeared to be a chronically ill, poorly developed, malnourished Negro girl in a moribund condition. A small, tender and fluctuant lesion 3 cm. in diameter was located over the left occipitoparietal area. A similar lesion measuring 3.5 cm. in diameter was present over the right occipitoparietal region. A subcutaneous mass measuring 4.5 cm. extended from the inferior portion of the right ear to the lateral aspect of the mandible and neck; the overlying skin was erythematous, warm and slightly tender to palpation. Another lesion, 2.8 by 5.1 cm., with a serpiginous and elevated border surrounding a crusted draining sinus was situated just inferior to the left eye. A small, grayish and fluctuant area was observed at the mid-point of the right upper eyelid. In addition, a 3.5 by 5.5 cm. subcutaneous swelling, both tender and fluctuant, was noted over the right lateral chest wall about 4 cm. below the axilla. Three draining sinuses surrounded by a flat, crusted area were located over the upper left scapula. A similar but smaller lesion was observed over the right scapula. Moderate swelling and exquisite tenderness of the left wrist were associated with a 1.5 cm. crusted lesion on the dorsal surface. The right elbow was swollen, tender and revealed a small draining sinus surrounded by a crusted area measuring 2 cm. in its greatest diameter. The right hip, right labium and entire right lower extremity were markedly edematous. This region was tender and any attempt at movement caused extreme pain. Three large draining ulcers surrounded the right patella. Four smaller but similar lesions were present over the medial and lateral portions of the right knee. Three additional sinuses were observed over the medial and lateral aspects of the right ankle. A single large ulcerative lesion was situated on the medial aspect of the left ankle; this was shallow, had a yellow, necrotic base and was surrounded by an elevated serpiginous edge. All sinuses and ulcers yielded a yellowish material which in some instances was quite thick but in others was of a serous character.

The mucous membranes were strikingly pallid. Aside from a sinus tachycardia of 160, cardiac examination was non-revealing. Physical examination of the lungs was difficult; however, moist inspiratory rales were detected over the left posterior lung field lateral to the heart. The

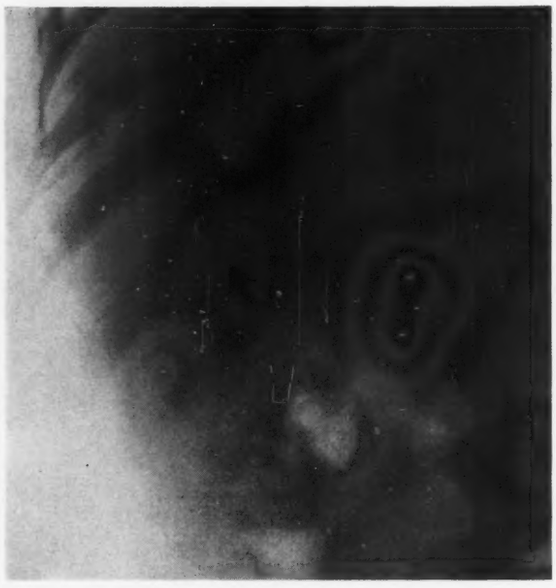
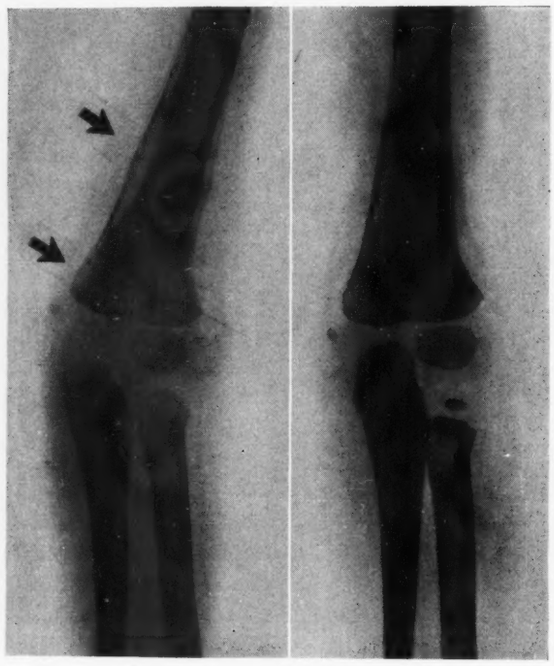


FIG. 4. Case II. Marked destruction of the tenth rib.

liver was palpated 2 cm. below the right costal margin and was non-tender. There was no splenomegaly. Palpation revealed tenderness over nearly all muscles and bones, especially in the extremities. The right clavicle was unstable in its mid-portion. Generalized, non-tender lymphadenopathy was present. Neuromuscular status could not be adequately evaluated, as any motion elicited cries of pain; at all other times the child lapsed into a semi-stuporous state.

On admission a biopsy of one cutaneous lesion was obtained. Likewise a sputum specimen and purulent material from one of the draining lesions were examined microscopically and were cultured on Sabouraud's medium at room temperature and on blood agar at 37°C. All preparations revealed B. dermatitidis. Very large numbers of these organisms were present in the biopsy specimen. (Figs. 3A and B.)

Roentgenologic studies disclosed a soft tissue mass in the left lower and mid-lung field as well as a diffuse, barely visible, nodular type of infiltration throughout both lung fields. Massive bony destruction was present immediately below the epiphyseal line of the right humerus; similar involvement was noted on the left. There was a fracture in the mid-shaft of the right clavicle. Osteolytic areas were noted in the right scapula. Marked destruction of the right tenth rib (Fig. 4) and less involvement of the right eighth rib was noted. Roentgenologic examination of the right elbow disclosed massive destruction



5A 5B

FIG. 5. Case II. A, three months after beginning 2-hydroxystilbamidine treatment massive destruction of the posterior portion of the lower right humerus with periosteal elevation was still present. B, marked improvement seven months after the initiation of therapy.

in the posterior aspect of the lower shaft of the humerus with periosteal elevation. (Fig. 5A.) There was also coarsening of the trabecular pattern in the upper shaft of the ulna. Similar studies of the skull revealed a large osseous defect with a serrated margin measuring 2.5 by 2.5 cm. (Fig. 6.) Another smaller bony defect was observed at the vertex on the left. Examination of the spine revealed complete destruction of the seventh thoracic vertebral body and osteolytic destruction in the third lumbar vertebra. Destructive changes were visualized in the capital epiphyses bilaterally, in the right ischium, left ilium and the left sacroiliac joint. Massive bony destruction was noted on the medial aspect of the lower shaft of the tibia on the left. (Fig. 7.) The right lower tibia disclosed periosteal proliferation together with marked bony involvement on the medial aspect and similar alteration of the epiphysis. A destructive lesion was described in the talus. In the left foot there were osteolytic changes in the calcaneus. Striking destruction of the lower shaft of the left radius with some sclerosis and quite marked periosteal proliferation were observed. (Fig. 8A.) Changes were also observed in the radial

FIG. 6. Case II. Large osseous defect in the calvarium.

epiphysis. Only three carpal bones were present, and shortening of the middle fifth phalanx was noted.

In view of the promising results of aureomycin therapy in previous cases of systemic North American blastomycosis administration of this antibiotic was immediately begun using 250 mg. every six hours. Forty-eight hours later 2-hydroxystilbamidine therapy was also instituted employing 28 mg. in 10 cc. of 5 per cent glucose intravenously each day. This medication was injected slowly over a twenty-minute period. Since no toxic effects were observed the quantity of 2-hydroxystilbamidine was increased after four days to 56 mg. every twenty-four hours; and eleven days later the dosage was further increased to 75 mg. daily. The same method of administration was employed.

Supplementary therapy consisted of a high protein, high caloric diet with added vitamins. Four transfusions of 200 cc. of whole blood were administered over a period of twelve days. Also, 0.3 gm. of ferrous sulfate was given three times a day

Aureomycin ointment and moist saline compresses were applied locally to all cutaneous lesions. Because of the marked pulmonary involvement and cough the patient was isolated. In view of the possible toxicity of prolonged therapy with 2-hydroxystilbamidine in a child, comprehensive laboratory studies were carried out: complete urinalysis daily, complete blood count and hematocrit every third day, hepatic function studies twice a week (cephalin-cholesterol flocculation, one minute and total serum bilirubin, prothrombin time and total and fractional protein determination), and blood urea nitrogen and blood non-protein nitrogen determinations twice a week.

The intravenous administration of 2-hydroxystilbamidine was continued for eight weeks; then, because of marked vascular sclerosis, treatment was discontinued for a week. Inasmuch as intravenous therapy was still difficult treatment was resumed using the same amount of 2-hydroxystilbamidine (75 mg.) intramuscularly in 2 cc. of 5 per cent glucose in normal saline containing 20 mg. of procaine. Since no significant tissue reaction occurred this method of treatment was employed daily for a week. Thereafter 2-hydroxystilbamidine was discontinued as the patient's condition had greatly

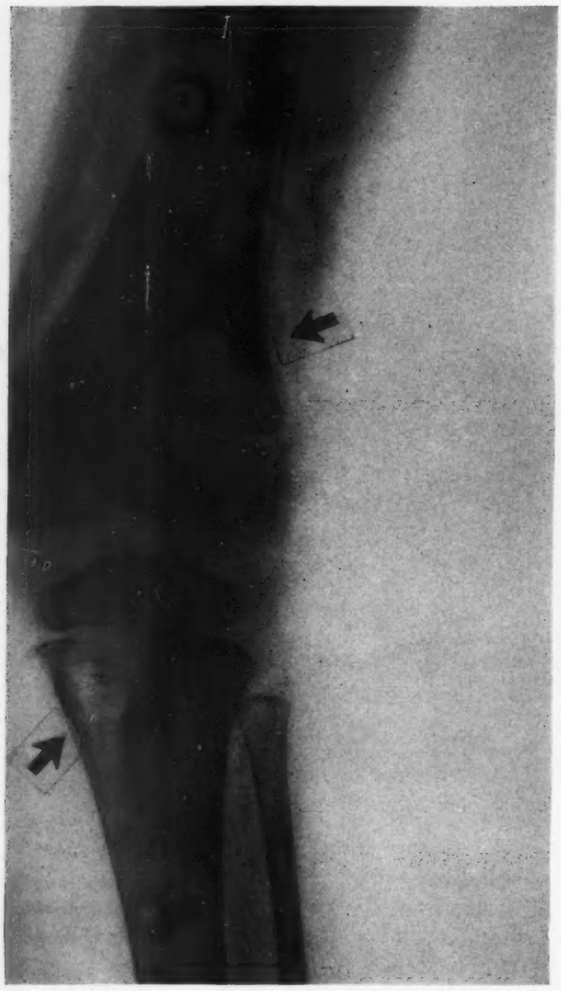


FIG. 7. Case II. Massive bone destruction of the lower femur and upper tibia.

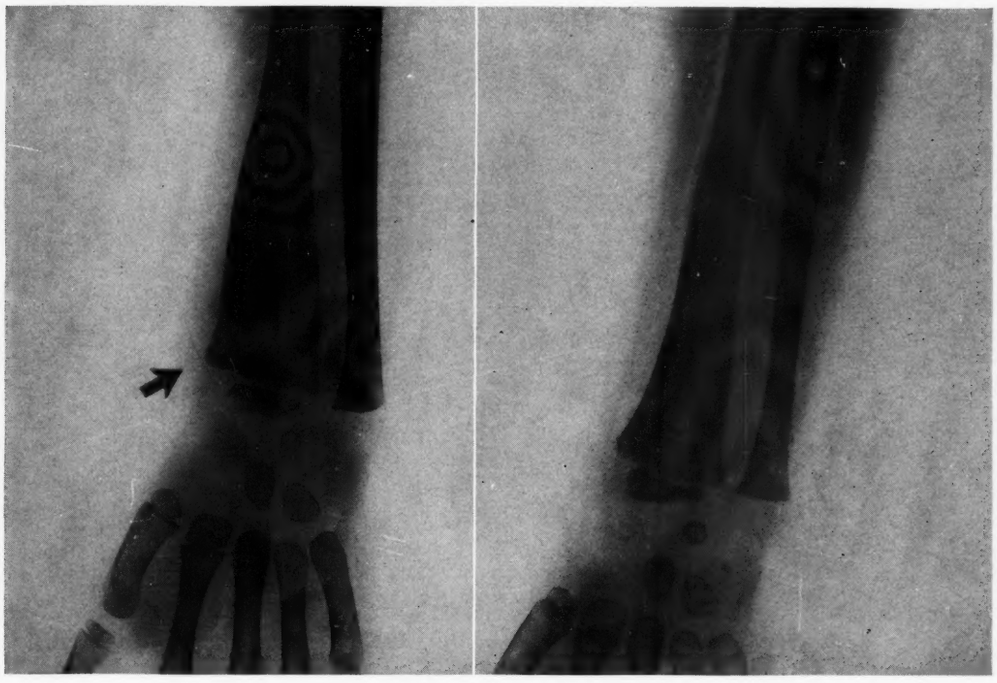
improved and medication was largely exhausted. However, aureomycin was continued and was increased to 1.2 gm. daily

For seven days after the institution of 2-hydroxystilbamidine and aureomycin treatment, the patient's temperature (rectal) ranged from 37.6°C. to 39.4°C.; then for the ensuing sixteen days it varied from 37.0°C. to 38.9°C.; thereafter, it remained within normal limits. Six weeks were required to attain persistently normal pulse values. One and a half weeks after hospitalization cough disappeared; within seven weeks all twenty-three cutaneous lesions had ceased draining and showed definite evidence of epithelization. Improvement of the lung involvement was established roentgenologically in eight weeks, although complete clearing required approximately seven months. Improvement of the bony involvement was quite gradual and the first definite evidences of healing were apparent only after treatment had been continued for three months. (Figs. 5B and 8C.)

After four and a half months all twenty-three cutaneous lesions had healed—only scarification marked their previous locations. The patient's weight had increased from 9.3 kg. to 12.2 kg. and the only remaining complaint was pain on motion of the right knee and hip. This knee could be extended approximately 140 degrees; any attempt at walking caused extreme pain in the region of the right hip and knee. Cultures of three sputum specimens and of three gastric washing preparations, as well as a biopsy specimen, were negative for B. dermatitidis. In addition, two biopsies failed to reveal these organisms in the tissue. On August 27, 1952, the child was discharged from the hospital. As a precautionary measure aureomycin was continued in the same dosage as before.

Four months after leaving the hospital (December 22nd) all of the cutaneous lesions had healed; weight had increased to 14.1 kg. (gain of 1.9 kg. since hospitalization). The child was asymptomatic, playful and able to hop about the house unassisted. The right knee could be extended approximately 160 degrees with full range of motion occurring at the right hip. The only abnormal test was hypoalbuminemia with continued hyperglobulinemia.

Laboratory data in this case were as follows: blood count: red cells ranged from 2,290,000 to 5,380,000; hemoglobin from less than 3.75 gm. to 11 gm.; hematocrit from 10 to 41 ml. per cent; white cells from 21,050 to 8,300; the initial differential white cell count revealed polymorphonuclear leukocytes 82 per cent, lymphocytes 16 per cent and eosinophils 2 per cent; but after May 2nd repeated differential counts were within normal limits; daily urinalyses revealed 1+ to a trace of protein together with hematuria (six to ten red blood cells per high power field of a centrifuged specimen) and pyuria (fifteen to twenty white blood cells per high power field of a centrifuged specimen) for the first six days of treatment but were within normal limits thereafter. The sedimentation rate (Wintrobe, corrected) ranged from 2.1 to 0.6 mm. maximal fall per minute (Rourke-Ernstene technic); the blood non-protein nitrogen from 24 to 41 mg. per cent, the blood urea nitrogen from 9.5 to 15.3 mg. per cent. As the condition of the patient improved the laboratory findings returned to normal. The total



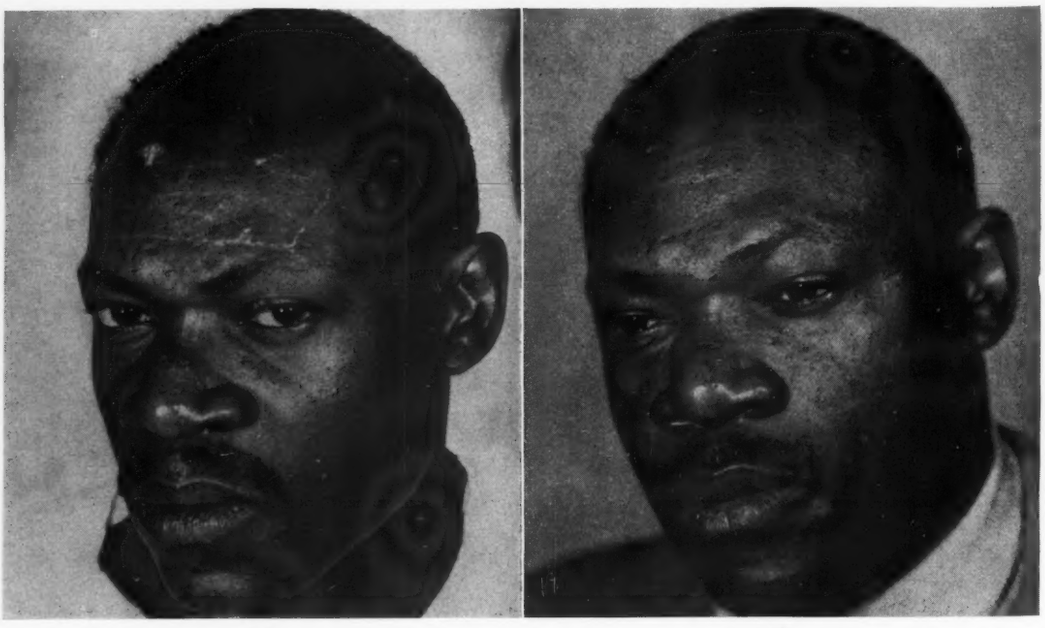
8A 8B

FIG. 8. Case II. A, bone destruction, some sclerosis and periosteal elevation of the left radius. B, marked improvement seven months after treatment with 2-hydroxystilbamidine was instituted.

serum protein increased from 5.7 to 7.4 gm. per cent, the albumin from 2.5 to 3.0 gm. per cent and the globulin decreased from 4.9 to 3.0 gm. per cent; prothrombin concentration changed from 51 to 100 per cent; cephalin-cholesterol flocculation test from 4+ to 1+ at twenty-four hours. The blood Kahn test was negative. Four blood cultures and a sternal marrow culture were negative for fungi and bacteria. The intradermal tuberculin test (PPD first and second strengths) was negative as were intradermal tests for histoplasmosis and coccidioidomycosis. *In vitro* sensitivity studies established a definite inhibitory effect by 2-hydroxystilbamidine on B. dermatitidis organisms isolated from this case. The sensitivity of this strain was comparable to that of strain E. I. (Table IV.)

Comment. The critical condition of this patient on admission and the probability of coexisting secondary infection were responsible for the decision to employ aureomycin together with 2-hydroxystilbamidine. The prognosis in systemic North American blastomycosis is always quite grave; when bone is diffusely involved, it is even worse.[44] Alfred and Harbin have emphasized that blastomycosis is one of the most common mycotic diseases of bone.[45] Although the response to treatment in this case has been most encouraging and no evidence of relapse has yet occurred, the prognosis must obviously be guarded. Only prolonged observation will determine the outcome. Additional treatment may well be necessary.

Of interest in this case were the serial serologic studies. Before treatment marked reactions were obtained in the complement fixation tests with the blastomyces antigens. With the yeast-like cell antigen a titer of 72 was obtained and with the extract antigen a titer of 150. Definite reactions were also obtained with the histoplasma antigen: with the yeast-like cell antigen a titer of 44 occurred and with the extract antigen a titer of 14. On December 24, 1952, (four months after leaving the hospital) a titer of 61 was obtained in the complement test with the extract antigen of the yeast-like cells of B. dermatitidis; a reaction which was not typical and could not be evaluated occurred with the yeast-like cell antigen. No reaction was obtained with the extract antigen of the yeast-like cells of H. capsulatum, although an atypical reaction which could not be evaluated occurred with the yeast-like cell antigen. It is interesting to note in this connection that the intradermal skin test for histoplasmosis was negative after the initial serologic studies. These findings, therefore, sug-



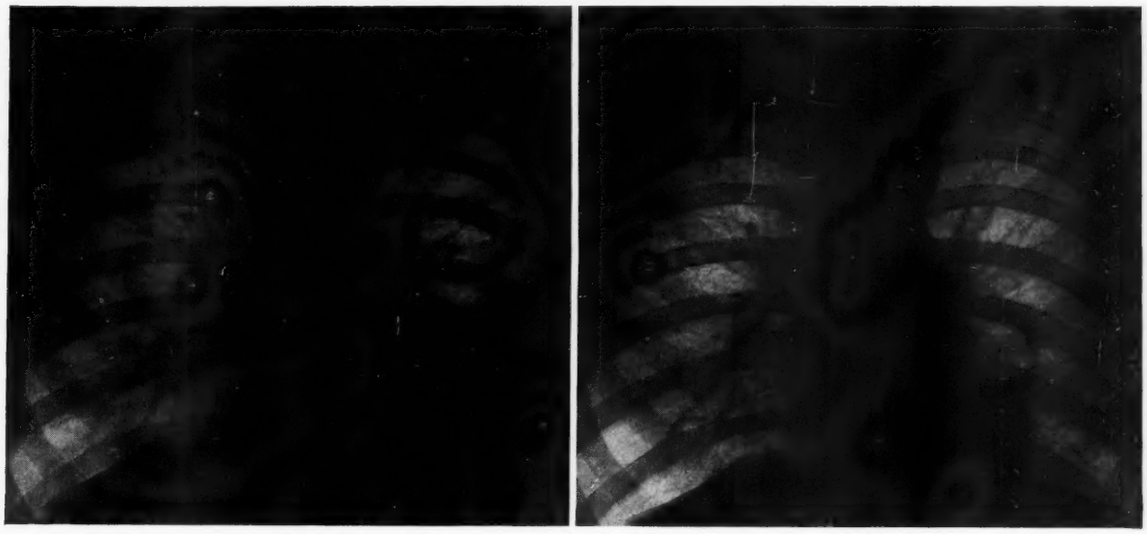
9A 9B

FIG. 9. Case III. A, blastomycotic lesions of the scalp, forehead, eyelid, nose and lip before treatment. Lesion on forehead had recently been biopsied. B, improvement after 2-hydroxystilbamidine therapy.

gest a serologic cross reaction between H. capsulatum and B. dermatitidis. Since the spread of blastomycosis is uncertain, complement fixation tests were carried out on this patient's immediate family—father, mother and two brothers (aged six and two years, respectively). All were negative except her younger brother with whom she played quite frequently. In his case a slight reaction of doubtful significance was obtained with the extract antigen but none with the yeast-like cell antigen of B. dermatitidis. Atypical reactions which could not be evaluated were also obtained with the two antigens in the test for histoplasmosis.

CASE III. A twenty-nine year old Negro man (F. A.) was admitted to the Medical Service of the John Gaston Hospital on September 5, 1952, because of hemoptysis, cough and chest pain.

During the first week of July this patient noted the onset of pain in the left lower chest accompanied with cough. The pain was of a pleuritic type and increased on deep inspiration. For approximately one week the cough was productive of only a small amount of mucoid material; thereafter, moderate hemoptysis developed. A private physician administered four intramuscular injections of penicillin without effect. The pain, cough and hemoptysis were still present at the time of hospitalization. Approximately ten days following the onset of pain in the chest a cutaneous lesion was noted on the upper left eyelid which was thought by the patient to be a sty. Using a needle he repeatedly attempted to drain this inflammatory area without success. During the latter part of July a similar lesion developed on the mid-point of the upper lip; the following week an additional ulcer was observed on the forehead just below the hairline. About the middle of August comparable lesions appeared on the nose, scalp and right supraorbital region. None of these cutaneous ulcers were painful; all were moderately pruritic and slightly tender to palpation. Five days prior to hospitalization a tender and painful subcutaneous mass developed on the lateral aspect of the left thorax just below the costal margin in the anterior axillary line. Dyspnea on exertion was first noted about August 1st and became progressively more severe. Anorexia developed insidiously and became quite marked after the first of August. The patient's weight decreased from 103 kg. in June to 77.8 kg. on admission to the hospital in September. While no frank chills occurred, the patient often noted chilly sensations. Frequent headaches, malaise and general muscular aches were noted during August and September. A dozen 100,000 unit oral penicillin tablets were ingested a week prior to admission without effect.



10A 10B

FIG. 10. Case III. A, chest roentgenogram before treatment; patchy consolidation is present in the left lower lobe. B, seven and one-half weeks after beginning 2-hydroxystilbamidine; only thickened pleura persists.

The past history in this case was non-revealing. The patient had been employed as a farmer in West Tennessee until the fall of 1949. For eighteen months before admission to the hospital he had worked in a lumber yard performing manual labor.

At the time of hospitalization the temperature was 38°C., pulse 110, respiration 32 and blood pressure 130/60 mm. Hg. The patient did not appear acutely ill. Examination of the skin revealed seven lesions located on the left temporoparietal area of the scalp, slightly to the right of the midline of forehead and 2 cm. below the hairline, on the left upper eyelid, across the bridge of the nose and on the mid-portion of the upper lip. (Fig. 9A.) A tender, subcutaneous mass 8 by 5.5 cm. was present 1.5 cm. below the left costal margin in the anterior axillary line. All of the cutaneous ulcers were similar—all were reddish brown and all possessed elevated peripheral margins; using a hand lens minute abscesses could be observed in the margin in all cases. All were slightly tender to palpation, and all showed a slight amount of seropurulent discharge. Cardiac examination disclosed a sinus tachycardia of 110. Increased tactile fremitus, dullness to percussion, bronchial breath sounds and fine rales were noted over the left lower lung field. The anterior and posterior cervical lymph nodes were moderately enlarged and slightly tender.

Microscopic examination of concentrated sputum specimens treated with 10 per cent potassium hydroxide disclosed innumerable, doubly refractile, round to ovoid bodies with granular cytoplasm measuring 7 to 10 μ in diameter. Cultures of the sputum and gastric washings revealed B. dermatitidis. A biopsy of one facial lesion disclosed B. dermatitidis on microscopic examination and on culture. Roentgenographic studies were interpreted as disclosing patchy consolidation in the left lung base (Fig. 10A); no bone or joint involvement was noted. Using enriched Sabouraud's media, B. dermatitidis was cultured from the blood stream.

Because of the excellent results obtained in the preceding cases 2-hydroxystilbamidine therapy was begun on September 22, 1952. Initially 0.11 gm. was given intravenously in 20 cc. of 5 per cent glucose in normal saline over a period of twenty minutes. No toxic effects were observed; therefore, after four days medication was increased to 0.225 gm. daily administered in the same manner as before. A low protein and low purine diet was employed. During the first week of treatment the weight decreased 4 kg. However, the patient became afebrile and drainage from the cutaneous ulcers largely disappeared. Likewise, the subcutaneous mass decreased to 60 per cent of its original size and became much less tender. In the course of the second week of 2-hydroxystilbamidine night sweats subsided, appetite increased, and there was a weight gain of 2.3 kg. At this point slight but definite clearing of the chest roentgenogram was reported. Marked improvement of the

cutaneous lesions was observed during the third week; the subcutaneous mass entirely disappeared and further clearing was evident in the chest film. However, sputum specimens obtained on October 13th were positive on culture for blastomyces (two and a half weeks after the institution of 2-hydroxystilbamidine therapy).

By November 12th the chest roentgenogram revealed only thickened pleura. (Fig. 10B.) The cutaneous lesions had entirely epithelized and only pigmentation and scarring remained. (Fig. 9B.) Weight had increased to 84 kg. (an increase of 6.3 kg. since hospitalization) and three specimens of sputum and gastric washings were negative for B. dermatitidis by microscopic and cultural studies.

From September 22nd to November 14th, a period of fifty-two days, the patient received 8.1 gm. of 2-hydroxystilbamidine administered by the intravenous route. On two occasions (totalling sixteen days) it was necessary to omit medication because the supply was exhausted. No toxic effects were observed. The patient was discharged from the hospital on November 20th in a completely asymptomatic state.

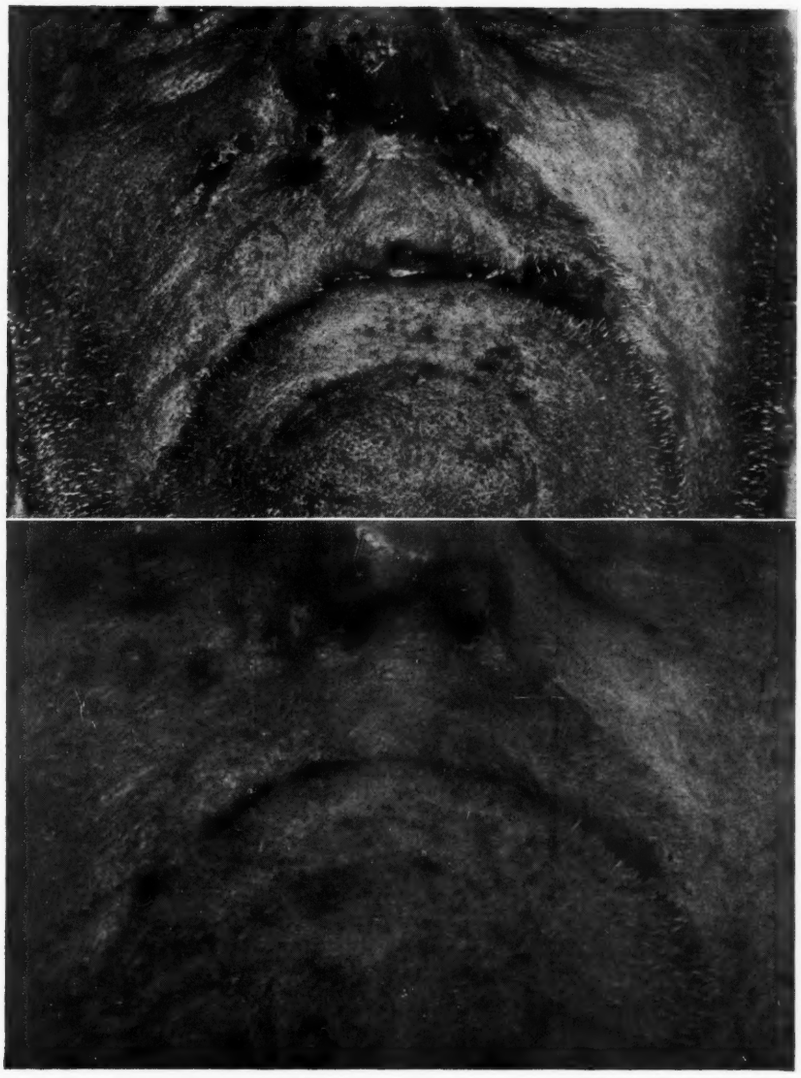
Serial serologic examinations in this case were especially interesting. Before the institution of treatment reactions were obtained with the two blastomyces antigens in the complement fixation test. However, exact titers could not be determined since the results were not entirely typical. On October 27, 1952, a slight reaction, titer 5, was obtained with the extract antigen of B. dermatitidis but none with the yeast-like cell antigen. Repeat studies on November 24, 1952, revealed no reaction with either antigen.

Laboratory data in this case were as follows: blood count: red cells ranged from 4,150,000 to 4,350,000; hemoglobin from 12 to 15 gm.; hematocrit from 40 to 47 ml. per cent; white cells from 15,750 to 4,750; a differential white cell count before therapy revealed 1 per cent metamyelocytes, 5 per cent stab cells, 85 per cent segmented cells, 1 per cent eosinophils, 1 per cent basophils, 1 per cent monocytes, and 6 per cent lymphocytes; subsequently all differential white counts were within normal limits; the initial urinalysis revealed 2+ proteinuria; thereafter only a trace was present. The blood non-protein nitrogen varied from 30 to 35 mg. per cent. As the clinical condition of the patient improved the laboratory findings returned to normal. The sedimentation rate (Wintrobe, corrected) ranged from 1.2 to 0.4 mm. maximal fall per minute (Rourke-Ernstene technic). The total serum protein increased from 6.8 to 7.5 gm. per cent, the albumin from 3.2 to 4.6 gm. per cent, and the globulin decreased from 3.6 to 2.9 gm. per cent; the prothrombin concentration changed from 39 to 74 per cent; the cephalin-cholesterol flocculation test from 3+ to 0 in twenty-four hours; two determinations of bromsulfalein retention (after forty-five minutes using 5 mg. per kg. of body weight intravenously) yielded normal values; the blood Kahn test was negative. The intradermal tuberculin test (PPD first strength) was negative at forty-eight hours but was 4+ using PPD second strength at forty-eight hours; the intradermal tests for histoplasmosis and coccidioidomycosis were negative. Spinal fluid studies before treatment were non-revealing. Serial electrocardiograms remained within normal limits and six blood cultures were negative for fungi and bacteria. *In vitro* studies established a definite inhibitory effect of 2-hydroxystilbamidine on B. dermatitidis organisms isolated from this case. The sensitivity of this strain was comparable to that of the strain E. I. (Table IV.)

Comment. Perhaps the outstanding feature in this case was the positive blood culture for B. dermatitidis. As far as can be ascertained from a review of the literature this is one of the few times that the fungus has been isolated from the blood. While prolonged follow-up will be required, the excellent clinical response and the remarkable improvement in the complement fixation tests are quite encouraging.

CASE IV. An eighty-four year old white man (C. C.) was admitted to the Medical Service of the John Gaston Hospital on February 28, 1952, because of chronic cutaneous lesions involving the nose and face.

The patient stated that in the spring of 1945 he noticed a small, painless, flat, erythematous papule in the region of the left nasolabial fold. An unsuccessful attempt at incision and drainage was followed by gradual extension with progressive involvement of both nares, the right and left nasolabial fold areas, both angles of the mouth and the right cheek. Various local preparations were applied without improvement. In 1946 a course of 400 roentgens was administered producing definite improvement for a period of six to eight months. However, in the spring of 1947 the patient's condition deteriorated and potassium iodide therapy was instituted. Medication was gradually increased until 40 drops



11A

11B

FIG. 11. Case IV. A, crusted blastomycotic lesion obstructing both nasal orifices and extending over the right and left nasolabial folds, the right cheek and both angles of the mouth. B, after 2.8 gm. of 2-hydroxystilbamidine, only erythema remained.

were administered three times a day; this regimen was continued for approximately six months, with marked improvement. Nevertheless, the lesions never completely healed and discontinuance of potassium iodide was followed by a severe exacerbation. In January, 1952, this man was referred to the West Tennessee Cancer Clinic with the clinical impression of basal cell carcinoma of the nose and lip. Biopsy established the diagnosis of blastomycosis and the patient was admitted to the John Gaston Hospital for treatment.

Upon hospitalization the patient complained of excessive dryness of the mouth resulting from forced oral respiration. Also, he had noted moderate pruritus associated with the cutaneous lesions. There was no pain, only a sensation of stiffness in the involved areas.

The past history was not revealing except for subtotal blindness resulting from trauma to the right eye fifty years previously. He had been employed as a farmer in West Tennessee for his entire life. Aside from the usual evidences of senility and the traumatic injury to his right eye, the only significant physical findings were related to the cutaneous lesions. (Fig. 11A.) Both nasal orifices were almost completely obstructed by a crusted brownish red lesion which extended over the right and left nasolabial folds. Smaller but similar areas were present over the

right cheek and both angles of the mouth, especially the left. Scarification had produced moderate deformity of the distal portion of the nose. Using a hand lens minute abscesses could be observed in the slightly elevated peripheral border of all the lesions. The margin of the large nasal ulcer was serpiginous in outline.

Following admission to the Medical Service a second biopsy was obtained for microscopic and bacteriologic study. In addition, a small amount of purulent material was obtained from a minute abscess by aspiration with a fine needle. B. dermatitidis was present in all specimens. Thorough investigation revealed no evidence of visceral involvement by blastomycosis.

Treatment with 2-hydroxystilbamidine was begun on March 4, 1952. Because of the patient's advanced age only 0.11 gm. was administered intravenously every other day. This was given slowly in 20 cc. of 5 per cent glucose over a period of twenty minutes. After two weeks medication was increased by giving the same dosage every day. By this time there had been definite objective improvement; also, pruritus had disappeared. By April 6th the patient had received 2.8 gm. of 2-hydroxystilbamidine and stated that he could breathe comfortably through his nostrils for the first time in four years; likewise, the upper lip was no longer "stiff." Treatment was continued until April 16th, with the patient receiving a total of 4.5 gm. of 2-hydroxystilbamidine.

Because of the patient's age blood pressure and pulse rate were recorded daily as well as before and after medication. In addition, comprehensive hematologic, renal and hepatic studies were obtained initially and thereafter twice a week. An electrocardiogram was obtained before, during and following treatment. The only definite evidence of toxicity occurred on one occasion when medication was injected rapidly (within one minute); almost immediately the patient complained of generalized pruritus, weakness and dizziness. Pallor and tachycardia (115 per minute) were noted. The blood pressure dropped from 120/60 mm. Hg to 98/44 mm. Hg but returned to initial levels within fifteen minutes. All other toxic manifestations disappeared within ten minutes. On two other occasions when medication was administered too rapidly (within five minutes) transient dizziness and headache were noted.

This patient was discharged on April 27, 1952, to be observed at monthly intervals through the Antibiotic Clinic. At this time only localized erythema marked the sites of the previous lesions. (Fig. 11B.) On December 22, 1952, (approximately eight months after the completion of therapy) no evidence of the previous cutaneous involvement could be detected. Even the erythema had disappeared.

Serial complement fixation studies in this case were extremely interesting. Using blood collected prior to therapy, no reaction occurred with the two blastomyces antigens. However, on April 18th a titer of 16 was obtained with the extract antigen of the yeast-like cells of B. dermatitidis, although there was again no reaction with the yeast-like cell antigen. Repeating these examinations on November 19, 1952, disclosed a very slight reaction, titer 3, with the extract antigen and once more nothing was observed with the yeast-like antigen.

Laboratory data in this case are as follows: peripheral blood studies: the hematocrit ranged from 39 to 43 ml. per cent; white cells from 4,600 to 11,300; repeated differential leukocyte counts were within normal limits. Daily urinalyses disclosed only proteinuria varying from 1+ to 2+. The sedimentation rate (Wintrobe, corrected) ranged from 0.4 to 0.6 mm. maximal fall per minute (Rourke-Ernstene technic). In the course of treatment the blood non-protein nitrogen decreased from 54 to 39 mg. per cent and the blood urea nitrogen from 24.3 to 11.9 per cent; the prothrombin concentration rose from 82 to 100 per cent; the total plasma protein from 5.8 to 7.4 gm. per cent, the serum albumin from 3.5 to 4.3 gm. per cent; the globulin decreased from 3.2 to 2.3 gm. per cent; the cephalin-cholesterol flocculation test from 2+ to 0 at twenty-four hours; total serum bilirubin from 0.8 to 0.5 mg. per cent; retention of bromsulfalein (after forty-five minutes using 5 mg. per kg. of body weight intravenously) before and after treatment was 5 per cent. The glucose tolerance test was within normal limits prior to and immediately following therapy. The blood Kahn test was negative. The intradermal tuberculin test (PPD first strength) was 1+ at forty-eight hours. Three sputum specimens and two gastric washing specimens were negative for tubercle bacilli and fungi. Three electrocardiographic tracings and two chest films were interpreted as showing no significant abnormalities.

Comment. As far as can be ascertained this is the oldest patient suffering from blastomycosis

reported in the literature. The response of the cutaneous lesions to 2-hydroxystilbamidine was excellent; complete healing occurred within two months. While the follow-up period in this instance is only eight months, this is the first time the patient has been entirely free of his illness since its inception. Complement fixation studies in this patient were quite interesting and also suggest a favorable prognosis. This case emphasizes the importance of slow and cautious intravenous administration of 2-hydroxystilbamidine.

OBSERVATIONS

Three concepts regarding blastomycosis are widely prevalent in medical circles. The first of these is that this disease is such a rarity that it need not be seriously considered in differential diagnosis. However, in a ten-year period sixteen patients with North American blastomycosis were observed at the John Gaston Hospital and the University of Tennessee College of Medicine; of perhaps even greater significance is the fact that seven additional cases were subsequently observed in the relatively brief period of fifteen months. Four of the latter patients came to necropsy diagnosed clinically as tuberculosis or bronchogenic carcinoma. Frequently, microscopic and bacteriologic examinations are necessary at autopsy to differentiate these diseases. It is quite probable that many cases of blastomycosis are misdiagnosed. This disease should be considered in all cases of chronic pulmonary disease simulating tuberculosis in which tubercle bacilli cannot be readily demonstrated. Numerous reports of blastomycosis have appeared in the recent literature and it is becoming more and more apparent that it is not as rare as many believe.

A second widely held view is that the diagnosis of blastomycosis is extremely difficult—that it requires prolonged and expensive laboratory procedures. Our experience indicates that the most important factor in the diagnosis of this disease is an awareness of its existence. Laboratory procedures involved, such as the microscopic examination of sputum and purulent exudates utilizing 10 per cent sodium or potassium hydroxide, the culture of body secretions, exudates and tissues as well as tissue biopsy, are not unusually difficult or expensive. Serologic studies are of value although their exact role in diagnosis does not appear to be definitely established. Two of our cases of systemic blastomycosis showed reactions to two histoplasma antigens although in much less degree than with the blastomyces antigens. Other investigators have obtained temporary reactions to blastomyces antigens in patients with active histoplasma infections.[46] In both instances intradermal tests for histoplasmosis were subsequently negative; in both cases the reactions disappeared after 2-hydroxystilbamidine had been administered. The possibility of cross reactions between B. dermatitis and H. capsulatum obviously must be considered. One patient in the present series (Case IV) had apparently suffered from cutaneous North American blastomycosis for seven years; yet he showed no reaction to the blastomyces antigens before treatment but immediately after therapy had a low titer of 1:16. Subsequently this was reduced without additional treatment to 1:3. Diagnosis in this instance had been established by tissue biopsy and by culture. The explanation for the serologic findings in this case is not clear but might be associated with the age of the patient (eighty-four years) or perhaps with the antigen employed. Isolated cutaneous blastomycosis is not always associated with a positive complement fixation test. In our cases we did not perform skin reactions with blastomyces antigens in order not to interfere with the serologic studies.

A third concept held by a large number of physicians is that the diagnosis of systemic North American blastomycosis is largely academic as no treatment is available and the death of the patient is usually inevitable. Until recently treatment has been limited to iodides and supportive therapy—adequate diet, vitamins, bedrest and general hygienic measures. While some have believed that potassium iodide is of value, others have denied this.[1,12,44] It has been demonstrated that aureomycin is capable of controlling this condition but apparently sufficient concentration cannot be obtained to eradicate the causative organism in the tissues, as is possible in actinomycosis.[2,47,48] The effect of cortisone in one patient (Case I) suggests that it is contraindicated in blastomycosis. The work of Schoenbach and his associates with stilbamidine led to the investigation of the possible use of the less toxic 2-hydroxystilbamidine in blastomycosis.[24–26]

Three cases of systemic North American blastomycosis and one case of the cutaneous form of this disease were treated with 2-hydroxystilbamidine. Included in this series are

an eighty-four year old man and a four year old child. The former apparently represents the oldest case reported in the literature; the latter is the only female in this series. In nineteen cases of blastomycosis observed at John Gaston Hospital only two were women. While the

TABLE II
COMPARISON OF THE SENSITIVITY OF B. DERMATITIDIS TO STILBAMIDINE AND 2-HYDROXYSTILBAMIDINE—S. B. STRAIN

		Mycelial Phase					
		Weeks after Inoculation					
μg. 2-OH Stilbamidine/cc.	μg. Stilbamidine/cc.	1	2	3	4	9	14
3.75	0	+	+±	+++	+++	++++	++++
0	3.75	++	+++	+++	++++	++++	++++
7.5	0	+	+	+	+++	+++	++++
0	7.5	++	++	+++	+++±	++++	++++
15	0	+	+	+	+	+++	+++
0	15	+	+±	++	+++	+++	++++
30	0	−	−	−	±	+	+
0	30	+	++	++	++	+++	++++
45	0	−	−	−	−	+	+++
0	45	+	++	++	++	++±	+++
75	0	−	−	−	−	+	+
0	75	+	+	+±	+±	++	++
750	0	−	−	−	−	−	−
0	750	−	−	−	−	−	−

follow-up period in these cases is short, objective and subjective improvement in all instances has been most encouraging, at times even dramatic. Prolonged observation will be required for definite evaluation of this method of therapy.

Even though treatment was extensive and prolonged no significant toxic effects were observed. It should be recalled that originally the customary dosage of stilbamidine administered to patients with leishmaniasis totalled about 2 gm.; even this quantity caused such severe trigeminal neuropathy that the use of this drug was discontinued.[38] Our experience obtained during the treatment of multiple myeloma with comparable doses of stilbamidine also emphasized the toxicity of this compound. In contradistinction, the four patients with blastomycosis reported here received 19.6, 4.3 (in a four year old) 8.1 and 4.5 (in an eighty-four year old) gm. of 2-hydroxystilbamidine, respectively. No trigeminal neuropathy developed and careful and extensive clinical studies did not reveal any other toxic sequelae, confirming previous observations. The same favorable result was recently described during the treatment of a case of South American mucocutaneous leishmaniasis with 6.1 gm. of 2-hydroxystilbamidine.[49]

Since such large doses of 2-hydroxystilbamidine can be given with impunity, diseases which until now have proved resistant to stilbamidine may be favorably influenced by larger doses of the 2-hydroxy derivative.

It is apparent (from Case IV) that 2-hydroxy-

TABLE III
COMPARISON OF THE SENSITIVITY OF B. DERMATITIDIS TO STILBAMIDINE AND 2-HYDROXYSTILBAMIDINE—D. U. STRAIN

		Mycelial Phase					
		Weeks after Inoculation					
μg. 2-OH Stilbamidine/cc.	μg. Stilbamidine/cc.	1	2	3	4	9	14
3.75	0	+	++±	++±	++++	++++	++++
0	3.75	++	+++	+++	+++	+++	+++
7.5	0	+	++	++	+++	+++	+++
0	7.5	++	++	+++	+++	+++	+++
15	0	+	+	+	+++	+++	+++
0	15	++	++	++	++	++	+++
30	0	−	+	+	+±	+±	+±
0	30	+	+±	++	++	+++	+++
45	0	−	±	±	±	+±	++
0	45	+	+	+±	++	++±	+++
75	0	−	−	−	−	+	+
0	75	±	+	+±	+±	++	++
750	0	−	−	−	−	−	−
0	750	−	−	−	−	−	−

TABLE IV
COMPARISON OF THE SENSITIVITY OF B. DERMATITIDIS TO STILBAMIDINE AND 2-HYDROXYSTILBAMIDINE—E. I. STRAIN

		Mycelial Phase					
		Weeks after Inoculation					
μg. 2-OH Stilbamidine/cc.	μg. Stilbamidine/cc.	1	2	3	4	9	14
3.75	0	+	+	+	++	++++	++++
0	3.75	++	++±	+++	+++	+++	+++
7.5	0	+	+	+	++	+++	+++
0	7.5	+	+	+	++±	++±	++±
15	0	−	−	±	±	+	+
0	15	−	−	±	+	+±	+++
30	0	−	−	−	−	+	+
0	30	−	−	−	−	±	+++
45	0	−	−	−	−	±	+
0	45	−	−	−	−	−	−
75	0	−	−	−	−	−	−
0	75	−	−	−	−	−	−
750	0	−	−	−	−	−	−
0	750	−	−	−	−	−	−

stilbamidine must be administered slowly if given by vein. It can be given intramuscularly without significant pain and tissue destruction, as first described by Sen Gupta.[50]

Initial test tube sensitivity studies were performed with a New York strain which was

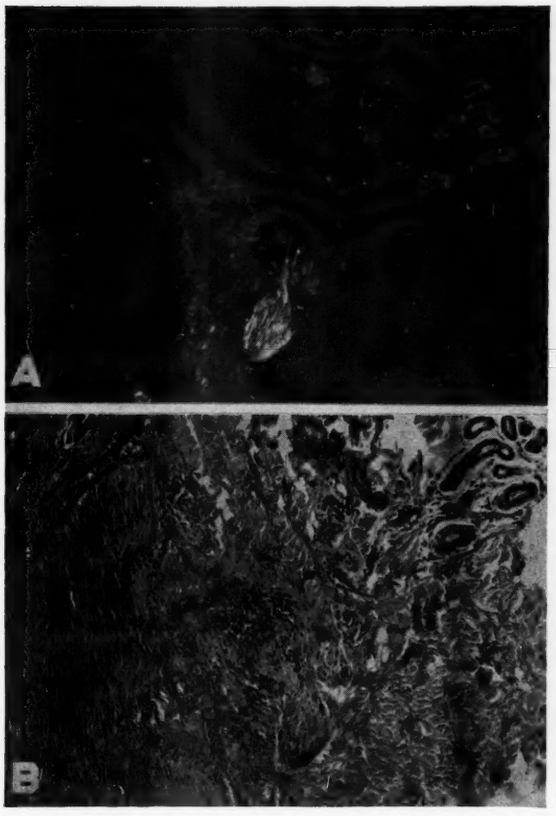


FIG. 12. Microscopic section of skin of patient with blastomycosis treated with 2-hydroxystilbamidine. A, section unstained, photographed with ultraviolet light. Sweat glands, inflammatory cells and nerve fiber strongly fluorescent. B, same section, photographed after staining.

FIG. 13. Nerve bundle present in Figure 14A, photographed with fluorescent light under higher magnification.

markedly sensitive to highly diluted solutions of both stilbamidine and 2-hydroxystilbamidine. (Table I.) A fungistatic effect on the mycelial and the yeast phase was evident when dilutions of 1 μg. per cc. of stilbamidine were used. Solutions containing 2 and 3 μg. per cc. did not permit growth even after incubation for one month. This strain was somewhat more resistant to 2-hydroxystilbamidine with the mycelial phase being slightly inhibited by 1 and 3 μg. per cc. and strongly so by 5 μg. per cc. The yeast phase showed inhibition with concentrations of 1 μg. per cc. Another strain (S. B.) disclosed a marked fungistatic effect, lasting three weeks, with 30 μg. per cc. of 2-hydroxystilbamidine but required more than 75 μg. per cc. of stilbamidine for similar results. (Table II.) Using a third strain of B. dermatitidis (D. U. strain) 45 μg. per cc. of 2-hydroxystilbamidine and more than 75 μg. per cc. of stilbamidine produced definite inhibition (Table III); while 15 μg. per cc. of both 2-hydroxystilbamidine and stilbamidine were required for another strain (E. I. strain). (Table IV.)

In vitro studies with two of our strains of B. dermatitidis did not suggest that the combination of 2-hydroxystilbamidine and aureomycin may act synergistically. At the same time no antagonistic action was noted. In view of our previous experiences, we believe that there may be some rationale in the clinical use of both drugs simultaneously in critically ill patients with disseminated blastomycosis since the antibiotic would be useful in combatting secondary infections.

It is well known that there is little parallelism between the fungistatic activity of a substance *in vitro* and its curative influence *in vivo*. Therefore, interesting as these test tube experiments are, relative resistance *in vitro* against stilbamidine or 2-hydroxystilbamidine does not rule out favorable clinical results. As an example the strain isolated from our first patient, S. B., may be mentioned. This blastomyces strain is remarkably resistant in the test tube. Marked fungistatic effect on the mycelial phase *in vitro* was obtained only when concentrations of

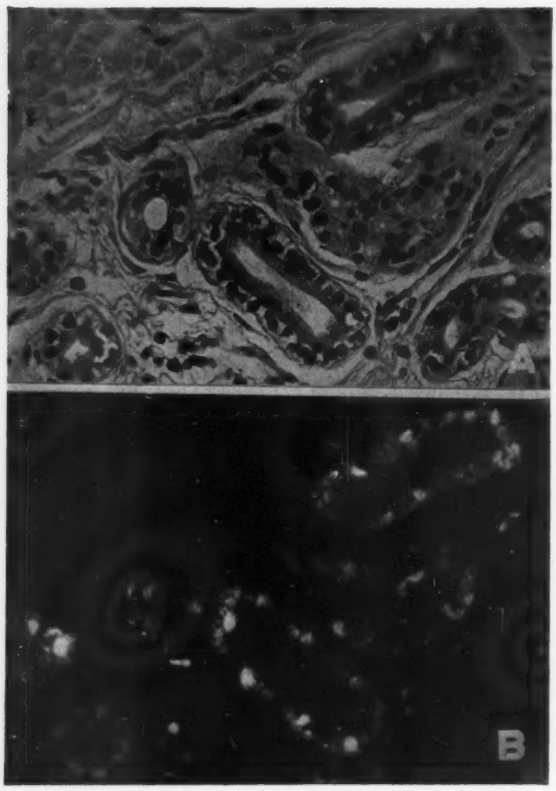


FIG. 14. Microscopic section of sweat glands of patient with blastomycosis, treated with 2-hydroxystilbamidine. A, photographed after staining; B, photographed unstained, with ultraviolet light.

30 μg. per cc. of 2-hydroxystilbamidine were used. Nevertheless, the administration of 2-hydroxystilbamibamidine rapidly cleared up the infection of the patient from which this strain was isolated.

Considerable amounts of stilbamidine and 2-hydroxystilbamidine are deposited in different organs and may remain there for many months after cessation of drug therapy. By fluorescent microscopy of histologic sections 2-hydroxystilbamidine can easily be demonstrated in the nuclei of many different organs.[51] Figures 12 to 14 demonstrate the presence of 2-hydroxystilbamidine in cutaneous epithelium, sweat glands, hair sheaths and adjoining sebaceous glands, subcutaneous nerve bundles and subcutaneous accumulations of inflammatory cells in blastomycosis patients treated with large amounts of this drug.

A substance like 2-hydroxystilbamidine which has a great affinity for nuclei[52] (Figs. 12–14) and which readily precipitates ribose- and desoxyribosenucleic acid in the test tube could presumably easily impair cell nucleus function. It may be noted that stilbamidine does not possess this affinity for nuclei to the same extent, although administration of both stilbamidine and 2-hydroxystilbamidine causes the formation of precipitates consisting of ribonucleic acid and either of the diamidines injected. It is, in fact, surprising that large amounts of 2-hydroxystilbamidine can be found in the cells without causing any disturbance in function.

SUMMARY

1. Three patients with proven systemic North American blastomycosis and one case of the cutaneous form of this disease were successfully treated with 2-hydroxystilbamidine.

2. Extensive clinical and laboratory studies revealed no definite evidence of toxicity resulting from the prolonged and extensive administration of 2-hydroxystilbamidine. In none of our cases did trigeminal neuropathy develop.

3. *In vitro* studies established a definite inhibitory effect of 2-hydroxystilbamidine on four strains of B. dermatitidis; 2-hydroxystilbamidine may be slightly more effective than stilbamidine on the mold phase of this organism.

4. In critical cases of systemic North American blastomycosis aureomycin may advantageously be combined with 2-hydroxystilbamidine in treatment.

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Histoplasmosis in Non-endemic Regions*

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HISTOPLASMOSIS was an unknown disease until 1906 when Darling[1] discovered the organism in histologic sections of a case diagnosed as leishmaniasis. He considered this hitherto unrecognized organism a protozoan, since it resembled closely Leishmania donovani, and applied to it the name of Histoplasma capsulatum. DaRocha-Lima[2] after reviewing these sections six years later was of the opinion that H. capsulatum was a fungus similar in nature to Cryptococcus farciminosus. However, it was not until 1932 when DeMonbreun[3] was able to isolate and cultivate the organism that its true fungous nature was clearly demonstrated and its morphology and cultural characteristics shown to be distinct from those of C. farciminosus.

At first histoplasmosis was recognized only on postmortem examination and this led to the belief that the disease was invariably fatal. The clinical manifestations considered characteristic of this condition were those of a severe systemic infection with high fever, progressive emaciation, anemia, leukopenia, generalized lymphadenopathy and enlargement of liver and spleen. At times extensive pulmonary involvement was noted which was indistinguishable from other forms of pneumonitis. Gastrointestinal ulcerations were common and were responsible for such symptoms as vomiting, abdominal pain and diarrhea. In addition it was noted that the adrenal glands were frequently involved by the disease process, resulting in clinical manifestations of adrenal insufficiency.[4] Macroscopically the individual lesions consisted of grayish white nodules which often contained necrotic centers and could not be distinguished from tubercles. Microscopically these nodules were found to consist of collections of large macrophages, the cytoplasm of which was filled with the yeast-like fungus.[5] In fatal forms of disseminated histoplasmosis the organism has been found in great numbers not only in the tissues but also in the wandering macrophages of the peripheral blood. The diagnosis has been established by isolating the organism on culture from sputum, gastric contents, peripheral blood, or material aspirated from bone marrow, spleen, liver and lymph nodes. Examination of biopsy specimens of lymph nodes or superficial lesions, when present, have been valuable adjuncts in arriving at the diagnosis.

H. capsulatum occurs in tissues as a round or oval shaped body averaging 2 to 4 μ in diameter, composed of a central granular mass of cytoplasm which is surrounded by a clear zone and refractile capsule. The yeast-like form will reproduce itself when inoculated onto blood agar and incubated at 37°C., while inoculation onto Sabouraud's glucose agar at room temperature results in development of the mycelial form.[6]

The fungus has been shown to occur naturally in many animals, including rats, skunks, ferrets, mice, cats and dogs.[7–9] It has also been isolated in pure culture from ticks that have fed on infected dogs.[8] Cultures of soil have likewise yielded the fungus.[10,11] Since infected animals excrete the organism in their saliva, sputum, vomitus, urine and feces, it is apparent that soil which has become polluted with the excreta of these animals will harbor the disease-producing organism. So far it has not been proved that animals may contract the infection from contaminated soil. However, it has been demonstrated that healthy dogs with negative histoplasmin skin tests will develop the infection following contact with both naturally and artificially infected dogs. On the other hand, transmission of the infection from dogs to human beings has not been noted even when contact has been close and prolonged.[9] Transmission of the disease from one person to another has likewise never been demonstrated. Evidence has been accumulating that inhalation of infected organic dust may be responsible for producing the disease in man,[11,12] indicating that the

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portal of entry is primarily through the respiratory tract. Invasion through the gastrointestinal tract has also been suggested as a common although less frequent mode of entry.[13]

For years after this new disease entity had been described it was recognized so infrequently that Parsons and Zarafonetis[14] on reviewing the literature in 1945 could find only seventy-one cases on record. Since 1945 a considerable change has taken place in the concept of the incidence and epidemiology of histoplasmosis. Largely due to the investigations of the U. S. Public Health Service[15–22] there has been amassed a great store of data indicating that in certain southwestern and southcentral states histoplasmosis can no longer be considered a rare, fatal disease, but rather a commonly occurring infection, usually benign and frequently asymptomatic during its acute phase. The first step in this direction was the observation that pulmonary calcifications in conjunction with negative tuberculin skin tests were a common phenomenon in certain areas. For a time these findings cast considerable doubt on the efficiency of the tuberculin test in detecting antecedent tuberculous infection and a hypothesis of anergy, caused by dying out of the infection, was proposed in order to explain this apparent loss of sensitivity to tuberculin. However, fungi were soon incriminated and sensitivity to histoplasmin was demonstrated in a high proportion of the negative tuberculin reactors with pulmonary calcifications. In the course of time the histoplasmin-positive, tuberculin-negative reactors with pulmonary lesions were shown to occur predominantly within an area incorporating the states of Tennessee, Kentucky, Arkansas, Missouri, Georgia and parts of Ohio, Illinois, Kansas and Oklahoma.[16,18,23–26] It may be readily understood, therefore, why histoplasmosis has been a common consideration in the differential diagnosis of pulmonary diseases in this endemic area but has rarely been considered seriously in the diagnosis of similar conditions in the eastern states. This view is reflected by the statement of one observer[27] that in Cincinnati the chances of pulmonary calcifications being due to H. capsulatum were 3:1 whereas 90 per cent of such roentgen findings in natives of New York City were attributable to tuberculosis.

However, arbitrary geographic boundaries cannot be regarded as the most significant factor in determining the prevalence of pulmonary histoplasmosis. Americans are accustomed to travel freely, both for pleasure and business reasons, and therefore many persons who are not natives of endemic states have visited and lived temporarily in such areas and have had ample opportunity for contracting the infection. In addition, during the recent war millions of our Armed Forces were dispersed throughout the United States and consequently a large proportion of them were stationed for varying periods of time in camps and training centers and were engaged in maneuvers and field exercises in states known to be endemic for histoplasmosis. In this way a significant segment of our present adult population in any part of the United States has had opportunity for infection with the causative agent of histoplasmosis. It is logical to expect, therefore, that many of the pulmonary lesions in adults residing in any part of the United States have been caused by infection with H. capsulatum incurred in an endemic area, without knowledge of this fact because of lack of associated symptoms. Months or years later these lesions may be detected for the first time in routine chest roentgenograms and may then pose diagnostic problems. The possibility that they may be tuberculous is usually the paramount consideration, although less frequently their appearance can suggest mediastinal tumors or pulmonary neoplasms. All too frequently, however, the possibility that these pulmonary lesions may have been caused by infection with H. capsulatum has been given scant consideration in non-endemic areas. This attitude of considering histoplasmosis only remotely in the problem of the differential diagnosis of pulmonary diseases in non-endemic regions will lead to diagnostic errors in a significant proportion of cases.

MATERIAL

Our experience at the Pulmonary Clinic of the Veterans Administration Regional Office, Brooklyn, New York, has borne out these concepts and has prompted this report. In the course of eighteen months we have accumulated a series of nineteen cases with pulmonary lesions, in which the histoplasmin skin tests were positive while the tuberculin and coccidioidin skin tests were negative. In addition we have discovered eighteen patients with similar pulmonary pathologic disorder on chest roentgenograms, in whom both histoplasmin and tuberculin skin tests were positive and the coccidioidin

skin tests were negative. The thirty-seven patients were examined at our clinic because of abnormal shadows discovered on chest roentgenograms taken either routinely or in the course of diagnostic study for complaints referable to the respiratory system. Difficulty in arriving at a definite diagnosis was experienced in these cases and led to skin testing. We wish to emphasize that all of these subjects were veterans, but only selected cases were studied in this way. This report therefore does not constitute a statistical analysis of the incidence of histoplasmosis in veterans. These thirty-seven persons have been under close observation for a minimum of one year, during which time no changes have been noted in their clinical status or in the appearance of the lesions on chest roentgenograms.

RESULTS

The observations in the histoplasmin-positive, tuberculin-negative series are summarized in Table I. In Table II are presented the findings in the histoplasmin-positive, tuberculin-positive series.

TABLE I

HISTOPLASMIN-POSITIVE, TUBERCULIN-NEGATIVE—NINETEEN CASES

Patient	Age	Birth Place	Time in Endemic Area	Illness in Endemic Area	Chest Roentgenograms	Hist.* (1:100)	O.T. (.01 and 1.0 mg.)	Cocc.† (1:100)	Complement Fixation Tests	
									Hist.‡	Bl.§
M. F.	29	N.Y.C.	Tenn. 10 mo.	"Virus pneumonia" 2 mo.	Multiple disseminated calcifications	+	−	−	−	−
C. S.	31	Ohio	Tex. 12 mo	None	1 by 1 cm. density left 7th anterior interspace	+	−	−	−	−
S. L.	29	N.Y.C.	Tenn. 1½ mo.	None	1½ by 1 cm. density right 2nd anterior interspace	+	−	−	±	−
A. S.	29	N.Y.C.	Tenn. 3 mo.	None	Right paratrachael lymph node enlargement (Fig. 4)	+	−	−	±	−
M. S.	38	N.Y.C.	Traveled through Tenn.	None	2½ by 2½ cm. density right 5th anterior rib	+	−	−	−	−
C. S.	23	N.Y.C.	Traveled by troop train east to west	None	5 by 5 cm. calcified mass left hilum	+	−	−	+	−
L. B.	36	N.Y.C.	Tenn. 1½ mo.	None	1½ by 1 cm. density left 5th anterior interspace	+	−	−	−	−
G. C.	28	N.Y.C.	Tenn. 6 mo.	None	1 by 1 cm. density right 6th anterior interspace	+	−	−	−	−
R. G.	52	Iowa	Tenn. 6 mo.	None	Fibrocalcific infiltration left upper lobe (Fig. 3)	+	−	−	−	−
H. K.	27	N.Y.C.	Tenn. 3 mo.	None	1½ by 1 cm. density right 4th anterior rib	+	−	−	−	−
R. W.	36	N.Y.C.	Okla. 12 mo.	"Undiagnosed pneumonia" 6 mo.	Multiple disseminated calcifications	+	−	−	+	−
E. S.	28	N.Y.C.	Ill. 2 mo.	None	Fibrocalcific infiltration right upper lobe	+	−	−	−	−
J. G.	40	Pa.	Ark. 12 mo.	None	Fibrocalcific infiltration left upper lobe	+	−	−	−	−
D. S.	31	N.Y.C.	Tenn. 3 wk.	None	Multiple disseminated calcifications (Fig. 1)	+	−	−	±	−
F. B.	42	N.Y.C.	Tenn. 12 mo.	None	1 by 1 cm. density right 4th anterior interspace	+	−	−	−	−
J F.	58	N.Y.C.	Passed through Okla.	None	Fibrocalcific infiltration right upper lobe	+	−	−	−	−
S. D.	37	N.Y.C.	Tenn. 1 mo.	None	1½ by 1 cm. density right 6th anterior interspace (Fig. 2)	+	−	−	−	−
T. M.	47	Pa.	Missouri 3 mo.	None	1½ by 1½ cm. density right 4th anterior interspace	+	−	−	−	−
D. F.	36	N.Y.C.	Tenn. 3 wk.	None	2½ by 2½ cm. right mediastinal mass	+	−	−	±	−

* Histoplasmin skin test 1:100
† Coccidioidin skin test 1:100
‡ Complement fixation test for histoplasmosis
§ Complement fixation test for blastomycosis

Histoplasmin-Positive, Tuberculin-Negative—Nineteen Cases (Table I)

Age: The age range was from twenty-three to fifty-eight years.

Nativity and travel in civilian life: Fifteen of the patients were born in New York City and had

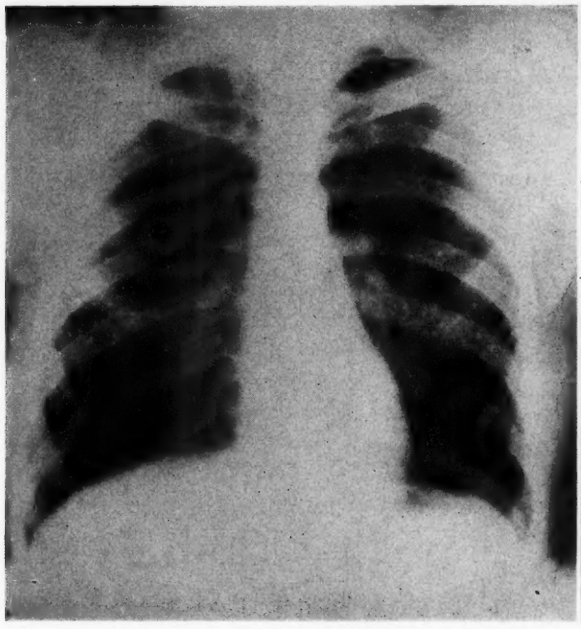

FIG. 1. Multiple disseminated calcifications; histoplasmin-positive, tuberculin-negative.

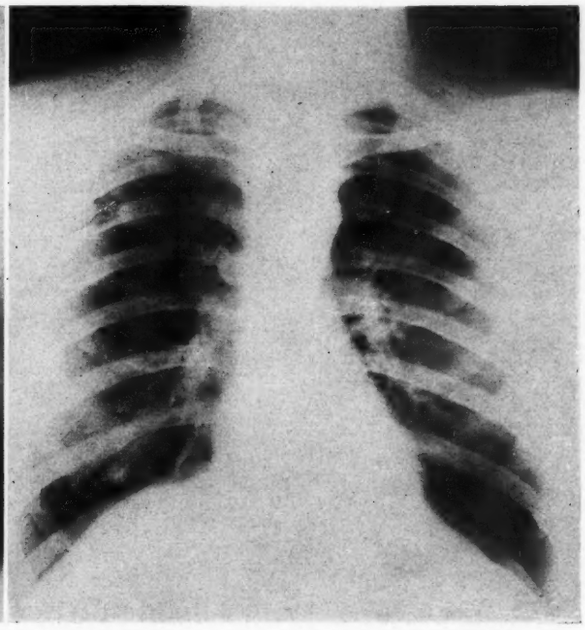

FIG. 2. One and one-half by 1 cm. density right sixth anterior interspace; histoplasmin-positive, tuberculin-negative.

resided solely in this locality except for their tour of military service. The remaining four were natives of Ohio, Iowa and Pennsylvania.

Travel in military service: In an effort to discover the environmental origin of the infection a careful inquiry was made into travel performed during military service, with special emphasis upon that carried out within the presently recognized endemic areas for histoplasmosis. Eleven veterans had been stationed in Tennessee for periods ranging from three weeks to one year, and one had merely "passed through" this state enroute elsewhere. One veteran had been stationed in Oklahoma for one year and another had "passed through" that state. Of the remaining five, one had resided in Missouri for three months, one in Arkansas for one year, one in Illinois for two months, one in Texas for one year, while one veteran, a native of New York City, gave no history of residence within any of the states known to be endemic but had travelled by troop train from the East to the West Coast.

After analyzing these histories of travel during military service it is interesting to note that the majority of these veterans had been stationed for a period of time in Tennessee, which is located in the heart of the endemic area for histoplasmosis. Others had lived for periods of time in Missouri, Oklahoma, Illinois and Arkansas, which are also well known endemic centers for this disease. One veteran had resided in Texas, which is adjacent to the endemic area. It is probable that in time mass x-ray surveys and skin testing will demonstrate that the endemic zone for histoplasmosis is much broader than presently recognized. Prolonged residence within the endemic area will naturally increase the possibility of infection with H. capsulatum. However, long residence in an endemic region is not essential in order to contract this infection, as demonstrated in one of these cases previously reported in which the known duration of exposure was only a period of hours.[12] Since it has been shown that coccidioides infection may be incurred by a person who merely travels through an endemic area by train,[28] it is possible that the infection with H. capsulatum in the veteran who had travelled by troop train from the East to the West Coast may have been contracted in a similar manner.

Chest roentgenograms: Four types of pulmonary lesions were noted. (1) Disseminated calcifications: Three persons demonstrated multiple disseminated calcifications of miliary or larger size. (Fig. 1.) Many of these lesions revealed the "halo" effect produced by the presence of a dense central core of calcification surrounded by a lighter, more radiolucent zone of fibrosis. In others the "halo" effect was absent since the

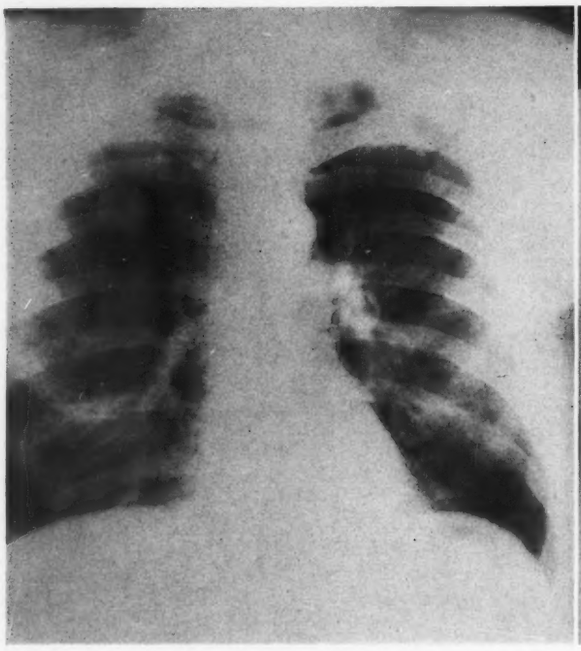

FIG. 3. Fibrocalcific infiltration left upper lobe; histoplasmin-positive, tuberculin-negative.

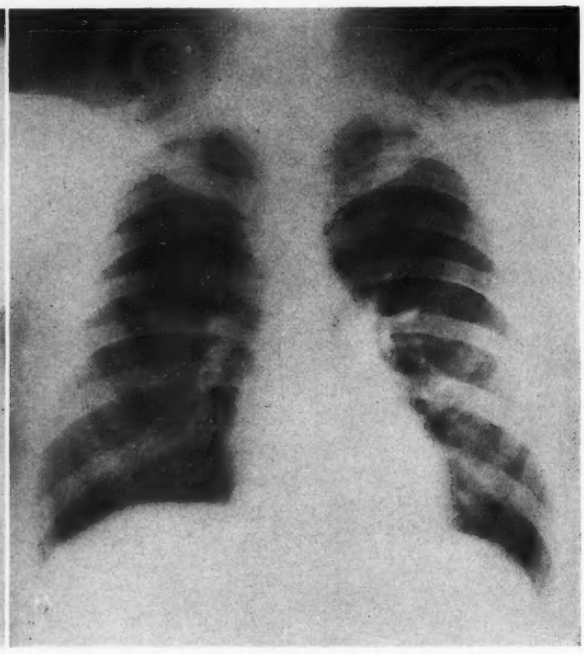

FIG. 4. Right paratracheal lymph node enlargement; histoplasmin-positive, tuberculin-negative.

lesions were completely calcified. Two of these individuals had had severe forms of "virus pneumonia" while stationed in the endemic zone. In both instances chest roentgenograms taken at that time revealed diffuse bilateral pneumonitis with hilar node enlargement, which gradually resolved, being replaced in several months by a fine, interstitial fibrosis. (2) Coin lesions: Well circumscribed, rounded densities measuring 1 to 2½ cm. in diameter were the most common roentgenographic findings, being present in nine of the subjects. (Fig. 2.) These lesions involved either lung field without predilection for any particular site. A central calcific deposit could be demonstrated in some, making them indistinguishable from tuberculomas. In others no calcium deposition could be noted, the lesions having a well defined appearance such as could be produced by any type of granuloma or neoplasm. (3) Infiltrations: Infiltrations in the upper third of the lung fields were noted in four persons. (Fig. 3.) The roentgenographic appearance of these infiltrations was typical of reinfection tuberculosis. In fact all of these patients had been referred to our clinic with the diagnosis of pulmonary tuberculosis and one of them had been hospitalized previously for twenty-four months in an institution for the tuberculous. (4) Mediastinal masses: Three patients revealed mediastinal lymph node involvement. (Fig. 4.) In one the chest roentgenogram revealed a calcified focus in the left lung field and a large, partially calcified mass 5 cm. in diameter in the region of the left hilum. In the second a 2½ by 1½ cm. right mediastinal mass with central calcification was present. Enlargement of the right paratracheal nodes, which had previously been attributed to sarcoidosis, was noted in the third.

Skin tests: The histoplasmin antigen employed in this study was of the lot H-42, a pooled lot comparing favorably with H-15, the previous standard.[29] One-tenth of 1 cc. of a 1:100 dilution was injected intracutaneously and the results observed in seventy-two hours. An area of induration at least 5 mm. in diameter was interpreted as a positive reaction. However, all individuals actually had intense skin reactions measuring more than 1 cm. in diameter. The tests did not produce systemic symptoms or cause apparent reactivation of the pulmonary lesions. The tuberculin skin tests employing first and second standard strengths of old tuberculin (.01 mg. and 1.0 mg. O.T.) as well as the coccidioidin skin tests in a 1:100 dilution were negative in all subjects. It has been shown experimentally that the histoplasmin skin test is highly specific and that the degree of cross reaction with related fungi is relatively small when

good antigens are used.[30] A positive skin test is therefore an indication of previous infection with H. capsulatum.

Complement fixation tests: The complement fixation tests for histoplasmosis were performed with both the yeast cell antigen of H. capsulatum and the extract antigen of the yeast-like cell. Two positive and four doubtful serologic reactions for histoplasmosis were obtained. The complement fixation tests for blastomycosis were negative in all.

TABLE II

HISTOPLASMIN-POSITIVE, TUBERCULIN-POSITIVE—EIGHTEEN CASES

Patient	Age	Birth Place	Time in Endemic Area	Illness in Endemic Area	Chest Roentgenograms	Hist.* (1:100)	O.T. (.01 and 1.0 mg.)	Cocc.† (1:100)	Complement Fixation Tests	
									Hist.‡	Bl.§
M. W.	42	N.Y.C.	Tenn. 12 mo.	None	1½ by 1½ cm. density right 6th anterior rib	+	+	−	+	−
Y. H.	37	Canada	Tenn. 7 mo.	None	1½ by 2 cm. density 4th left anterior interspace	+	+	−	±	−
R. G.	37	N.Y.C.	Tenn. 2 mo.	None	Fibrotic infiltration left upper lobe (Fig. 7)	+	+	−	−	−
J. F.	36	N.J.	None	None	2 by 2 cm. density left 6th anterior interspace	+	+	−	−	−
B. C.	33	N.Y.C.	None	None	2 by 1½ cm. density right 4th anterior interspace	+	+	−	−	−
H. R.	30	N.J.	Miss. 6 mo.	"Bilateral pneumonia" 2 mo.	Multiple disseminated calcifications	+	+	−	−	−
J. Z.	29	Pa.	Tenn. 10 mo.	"Virus pneumonia" 7 mo.	Multiple disseminated calcifications (Fig. 5)	+	+	−	+	−
D. G.	46	Italy	Tenn. 12 mo.	None	Multiple disseminated calcifications	+	+	−	−	−
S. Y.	38	N.Y.C.	Ga. 15 mo.	"Pneumonia" 1 mo.	Fibrocalcific infiltration right upper lobe	+	+	−	−	−
N. M.	35	N.Y.C.	Tenn. 2 mo.	None	2 large densities in each lower lobe, the largest 4 by 3 cm. (Fig. 6)	+	+	−	−	−
D. F.	38	N.Y.C.	Missouri 9 mo.	None	1 by 1 cm. density right 2nd anterior interspace	+	+	−	−	−
W. P.	26	Puerto Rico	Kan. 8 mo.	None	1½ by 1½ cm. density right 6th anterior rib	+	+	−	−	−
R. R.	41	N.Y.C.	Tenn. 12 mo.	None	1 by 1 cm. density right 6th anterior interspace	+	+	−	−	−
A. G.	49	Rumania	Ark. 8 mo.	None	1 by 1 cm. density left 4th anterior interspace	+	+	−	−	−
M. G.	35	N.Y.C.	Ky. 1 mo.	None	2 by 1½ cm. density right 5th anterior interspace	+	+	−	−	−
A. O.	26	N.Y.C.	Missouri 3 mo.	None	Multiple disseminated calcifications	+	+	−	±	−
M. B.	28	Pa.	Missouri 13 mo.	None	Fibrotic infiltration right upper lobe	+	+	−	±	−
A. S.	32	N.Y.C.	La. 12 mo.	None	1 by 1 cm. density right 1st anterior interspace	+	+	−	−	−

* Histoplasmin skin test 1:100
† Coccidioidin skin test 1:100
‡ Complement fixation test for histoplasmosis
§ Complement fixation test for blastomycosis

Histoplasmin-Positive, Tuberculin-Positive—Eighteen Cases (Table II)

Age: The age range was from twenty-six to forty-nine years.

Nativity and travel in civilian life: Ten of the patients were born in New York City, two in New Jersey, two in Pennsylvania and one each in Canada, Puerto Rico, Rumania and Italy. With the exception of the foreign-born none had travelled far from their birthplace during civilian life.

Travel in military service: Seven had been stationed in Tennessee, three in Missouri and one each in Mississippi, Georgia, Kansas, Louisiana, Arkansas and Kentucky during their military service. No history of travel in the endemic area could be obtained in two persons.

Chest roentgenograms: The findings were essentially similar to those observed in the histoplasmin-positive, tuberculin-negative series. (1)

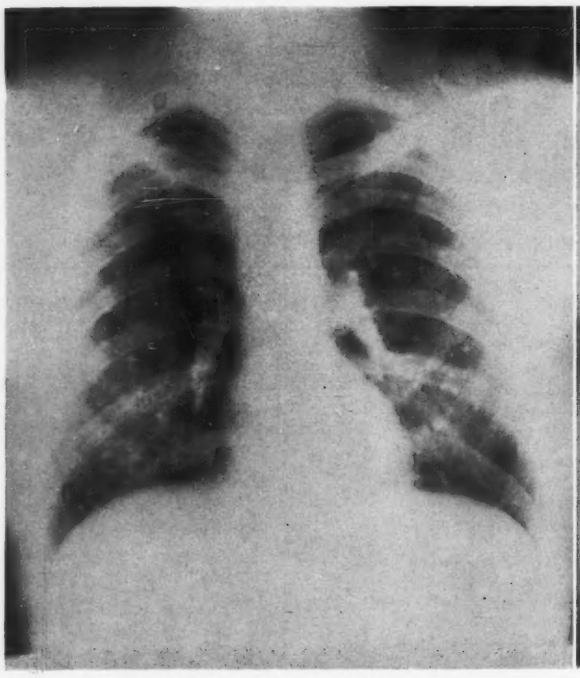

FIG. 5. Multiple disseminated calcifications. Histoplasmin-positive, tuberculin-negative.

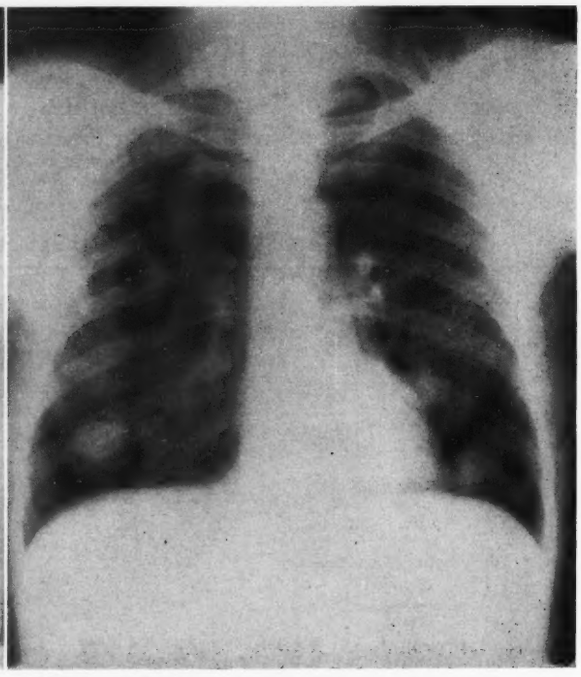

FIG. 6. Two large densities in each lower lobe, the largest 4 by 3 cm., histoplasmin-positive, tuberculin-positive.

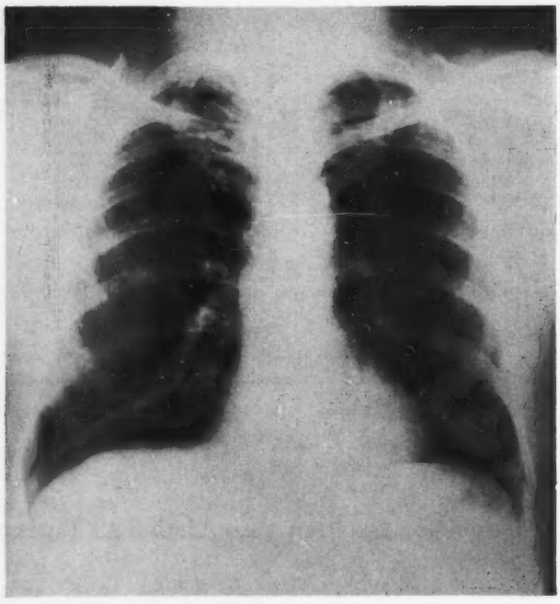

FIG. 7. Fibrotic infiltration left upper lobe; histoplasmin-positive, tuberculin-positive.

Disseminated calcifications: These were noted in four persons (Fig. 5), two of whom had been hospitalized for a prolonged period of time, while in the endemic area, for pneumonia of undetermined nature. (2) Coin lesions: These were noted in eleven subjects (Fig. 6) and were indistinguishable from similar lesions noted in the previous series. (3) Infiltrations: Pulmonary infiltrations were observed in three persons. These had the characteristics of reinfection tuberculosis. (Fig. 7.) (4) Mediastinal adenopathy: This was not noted in any members of this series.

Skin tests: The histoplasmin and tuberculin skin tests were positive and the coccidioidin skin tests were negative in all.

Complement fixation reactions: Two positive complement fixation reactions for histoplasmosis were obtained. Chest roentgenograms revealed disseminated calcifications in one and a coin lesion in the other. Three doubtful reactions were also obtained. In one, chest roentgenograms demonstrated disseminated calcifications, in the second an infiltration in the upper lobe of the right lung and in the third a coin lesion in the left lung.

In general, therefore, the pulmonary lesions in the two series were similar. In those having positive tuberculin skin tests as well as positive histoplasmin skin tests the cause of the pulmonary involvement cannot be definitely ascribed to infection with H. capsulatum. However, in view of the close parallel that exists between the two series it is highly probable that the lesions

in the histoplasmin-positive, tuberculin-positive series were due to histoplasmosis rather than to tuberculosis. In two of these persons there is confirmatory evidence in the form of positive complement fixation tests for histoplasmosis, and in three others there is suggestive evidence of this fact in the form of doubtful complement fixation tests for histoplasmosis. The complement fixation tests for blastomycosis, on the other hand, were negative in all subjects.

SUMMARY

In the past seven years it has become increasingly recognized that histoplasmosis is a frequent cause of pulmonary disease in endemic areas. It is the purpose of this report to show that histoplasmosis is also a common cause of pulmonary involvement in non-endemic regions.

Roentgenographically, histoplasmosis may simulate many forms of pulmonary disease. It is necessary, therefore, to perform skin tests with tuberculin, histoplasmin and coccidioidin routinely in the diagnostic work-up of pulmonary conditions if one is to detect histoplasmosis. The complement fixation test for histoplasmosis is of relatively minor importance in detecting inactive cases of this disease. It need only be performed in those individuals reacting to the histoplasmin skin test, in whom a positive serologic reaction can serve as confirmatory evidence of the presence of histoplasmosis.

We believe that cases of histoplasmosis will be discovered in increasing numbers in non-endemic regions, in proportion to the awareness of its varied manifestations and the zeal with which the search is made.

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Erythema Exudativum Multiforme*

Its Association with Viral Infections

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Erythema exudativum multiforme (EEM) was first clearly described and differentiated from other dermatoses by Hebra in 1866.[23] It is ordinarily characterized by a relatively mild clinical course with few or no systemic manifestations and by polymorphous skin lesions which may be maculopapular or, less often, vesiculobullous in appearance. In contrast to this benign condition, uncommon instances of an acute, often severe illness occur and pursue a pronounced febrile course accompanied by severe constitutional symptoms and by similar, though more severe, inflammatory lesions of the skin, eyes, genitalia, and mucous membranes of the oropharynx, respiratory tract, colon and rectum. The unusual character of these cases has led observers to describe them as newly recognized diseases and a confusing terminology has thus arisen. Depending upon the predominant manifestations, the syndrome has been designated ectodermosis erosiva pluriorificialis (Rendu[38]), dermatostomatitis (Baader[7]), eruptive fever with stomatitis and ophthalmia (Stevens and Johnson[48]), and the mucosal respiratory syndrome (Stanyon and Warner[46]). Behçet's syndrome, ulcus vulvae acutum (Lipschütz) and Reiter's syndrome are probably related diseases.[39] These conditions are now generally regarded as unusual manifestations of EEM and, in an effort to clarify confusing nomenclature, Ashby and Lazar[6] make the pertinent suggestion that the fulminant type of the disease be designated EEM Major, the term EEM Minor being used for the mild types originally described by Hebra.

No single specific cause of EEM is known. It appears likely that the disease is an expression of allergy or hypersensitivity to many incitants. Apparently it may at times be initiated by drugs. For example, some instances of the major type have seemed clearly related to the administration of sulfonamides.[6] The character of the lesions and the striking systemic manifestations suggest that EEM Major may be an infection. Numerous attempts to isolate specific bacteria have yielded variable and inconsistent results. Recently interest has centered upon a possible relationship of EEM Major to viral infections. It is the purpose of this communication to review briefly some studies bearing upon this relationship and to report a case of EEM Major in which herpes simplex virus was isolated.

PREVIOUS VIROLOGIC INVESTIGATIONS

Foot and Mouth Disease. EEM Major and the human form of foot and mouth disease have striking similarities. However, Baader[7] and Klauder[28] were unsuccessful in isolating the virus of foot and mouth disease by inoculation of guinea pigs with materials from patients with EEM.

Mumps. The development of EEM Major was preceded by mumps in a case described by Edgar and Syverton.[18] No intracellular inclusions were seen in histologic sections of the patient's skin lesions and attempts to isolate an infectious agent by animal inoculation failed. Kove[31] also described an instance of EEM Major occurring shortly after the development of mumps. No attempts to isolate a virus were made.

Contagious Pustular Dermatitis (Orf). Human infections with the virus causing this disease of sheep occur rarely. In at least one instance[8] a human infection, proved by the isolation and identification of the virus, was accompanied by EEM Minor involving the upper extremities. The virus presumably has not been implicated in cases of EEM Major.

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Ill-defined or Newly Recognized Viruses. Alm and Öberg[1] inoculated rabbits intracisternally and intra-ocularly with spinal fluid and Berkefeld-filtered sputum from three cases of Behçet's syndrome. The animals variously developed encephalitis, optic neuritis, retinitis, uveitis, bullous keratitis and conjunctivitis. It was possible to produce these lesions in rabbits through four serial passages whereas injections of normal rabbit tissue failed to produce disease in control animals.

Viruses Producing "Atypical" Pneumonia. "Atypical" pneumonia occurs not uncommonly as an accompaniment of EEM Major. It was observed in approximately 30 per cent of the cases collected by Ashby and Lazar.[6] The pneumonia in many of these instances has been identical clinically with "primary atypical pneumonia of unknown etiology," and rising titers of cold hemagglutinins have been demonstrated in the sera of many of the patients. However, no satisfactory evidence has been presented to support the suggestion[29,53] that the agent or agents causing primary atypical pneumonia may be directly related to the development of severe EEM.

Atypical pneumonia was present in many of the cases of EEM which were described by Stanyon and Warner[46] as the "mucosal respiratory syndrome." These authors stated that viruses had been isolated from two cases by animal inoculation of vesicle fluid, blood, sputum and tissues obtained at necropsy. Additional observations, however, failed to confirm these findings.[47] Likewise, in studies of EEM with atypical pneumonia made by the Commission on Acute Respiratory Diseases[15] during World War II, materials from five cases, including the lung of a fatal case, were inoculated into a wide variety of animals, including monkeys and chick embryos, with negative results.

Two groups of workers have presented serologic evidence suggesting that psittacosis virus, which is known to produce an "atypical" pneumonia, may be implicated in the development of EEM Major. Serum obtained by Jones and others[25] in the fifth week of disease from a patient with EEM Major contained complement fixing antibody against psittacosis antigen in dilution of 1:32 (4+) and 1:64 (3+). These workers were unable to demonstrate inclusion or initial bodies in scrapings from the eyes and urethra. In a study of two additional cases they likewise failed to demonstrate inclusion bodies in conjunctival and vaginal scrapings.[24] Sera obtained at two, five and ten weeks of illness in the first case contained no antibody against psittacosis virus but the complement fixation test for psittacosis in the second case was positive in dilution of 1:2 (4+) and 1:4 (1+) with serum drawn during the second week of illness. Finland and associates[17] studied four cases of EEM Major with atypical pneumonia, three coming to autopsy and one surviving. Two of the patients gave a history of exposure to sick birds but the serum of only the individual who survived contained complement fixing antibody against psittacosis virus. The titer in this instance rose from 1:2 (2+) in the first week to 1:16 (4+) and 1:32 (3+) in the fifth week. An additional fatal case with no known contact with sick birds showed a titer of 1:256 (4+) in the third week of illness and 1:256 (4+) and 1:1024 (2+) six days later. Examination of sputum, vesicle fluid, and the lungs and other tissues of the fatal cases showed no elementary or inclusion bodies. Attempts to isolate psittacosis or other viruses from the lungs in the fatal cases were unsuccessful except in one instance in which herpes simplex virus was demonstrated.

Herpes Simplex. The association of EEM with herpes simplex infections has been of considerable interest to a number of observers. The association was first emphasized by Urbach[51] and the clinical relationship of the two diseases has been confirmed by a number of additional observations.[4,18,34,36,40,49,50,52,53] However, few cases of EEM have been adequately investigated by attempts at virus isolation and by immunologic studies either to establish or disprove the presence of herpetic infection.

1. *Negative or inconclusive investigations:* Despite the presence of certain clinical features suggesting herpetic infection in their patients with EEM Major, Koke,[30] Bradlow and Schless,[11] and Givner and Ageloff[20] were unable by animal inoculation to isolate a virus or by serologic studies to implicate herpes simplex virus. Likewise, in a recent evaluation of the complement fixation test in the diagnosis of herpetic infections Gajdusek and associates[19] were unable to demonstrate a rise in antibody titer in sera obtained from three patients during the course of EEM Major, although some antibody was present in one instance. Material from a patient described by Soll[45] produced plaques on the chorio-allantoic membrane of embryonated eggs in three separate experiments of five, three and fifteen passages; however, their production

was variable and unpredictable, they differed from those ordinarily produced by herpes simplex virus and their formation was not inhibited by the patient's serum obtained during convalescence. Neither the original materials from the patient nor the lesion-containing membranes produced disease upon inoculation into mice or other laboratory animals. The patient's serum and that of three additional cases of EEM Major contained no neutralizing antibody for herpes simplex virus by titration in mice.

Anderson[2] studied three individuals with EEM Major. In one case materials from lesions of the mouth and penis produced in rabbits a mild keratoconjunctivitis lasting seventy-two hours. Intracerebral passage of material from the rabbit eye to mice gave inconclusive results. Titration of the patient's serum specimens against the HF strain of herpes simplex in mice showed a ten- to one-hundred-fold increase in antibody titer. Vesicle fluid from a second patient produced a transient, mild opacity of the rabbit cornea, and paralysis of the lower extremities occurred in guinea pigs in the fourth week after intracerebral inoculation. The patient had developed a rise in antibody against herpes simplex to more than 1,000 protective units per 0.5 ml. of serum by the twenty-third day of illness; however, only a ten-fold increase was present at fifty-three days. Anderson concluded that the agent isolated was not herpes simplex in view of the fact that it had many qualities which were "distinctly different." The third case, a six and one-half year old child, developed EEM Major two weeks after exposure to his father who had a severe episode of recurrent herpes simplex. Vesicle fluid obtained on the third and fourth days of illness produced severe keratoconjunctivitis in rabbits within seventy-two hours. Washings from the eyes were passed to other rabbits with similar results; however, washings from the latter failed to produce encephalomyelitis in mice and guinea pigs. The corneal epithelium of the rabbits was described as showing acidophilic, *intranuclear* inclusions; however, the details of this case study, published elsewhere,[3] vary from this description and are not compatible with herpetic infection. Indeed, inclusions were not seen in hematoxylin and eosin preparations, were observed only in specially stained sections and, unlike the inclusions of herpes simplex, were described and pictured as being *intracytoplasmic* in location. Serum from a rabbit recovering from keratoconjunctivitis (thirteenth day) contained no neutralizing antibody for the HF strain of herpes simplex as titrated in mice. Neutralizing antibody levels were not determined in the patient's serum. It is of interest that Hanke[21] observed similar cytoplasmic inclusions in materials from a case of EEM Major.

2. *Studies yielding herpes simplex virus:* On two occasions investigations have yielded apparently acceptable evidence implicating herpes simplex virus in the pathogenesis of EEM Major. Sanders,[43] using tissue cultures and mouse inoculation, isolated from the sputum of a case of EEM with atypical pneumonia a "variant of herpes simplex" producing a fatal encephalitis but yielding no pneumonic lesions in mice. Further details of this study were not given and no serologic studies were noted. Finland and associates,[17,33] although failing to isolate a virus from most of their cases of EEM Major with "atypical" pneumonia, were successful in obtaining herpes simplex virus from the lung of a fatal case whose serum contained no complement fixing antibody for psittacosis. The patient had been ill for over three weeks and no herpetic inclusions were evident in histologic sections of the lungs. However, even after prolonged storage this tissue infected mice when injected in a dilution of 10^{-2} and it was considered unlikely that the quantity of virus present could have resulted from contamination. Serum antibody against herpes was not determined in this case.

In view of the inconclusive or negative results of many of these previous virologic studies, additional evidence of the association of the virus of herpes simplex with EEM Major is of interest. Observations on a patient from whom herpes simplex virus was isolated and whose illness terminated fatally follow:

CASE REPORT

V. B. W., No. 140678, a nineteen year old white woman, was admitted to the Vanderbilt University Hospital for the seventh time on September 28, 1951. Her health had been good until age ten when she developed measles, which was complicated by pneumonia. After a prolonged illness of about three months she developed an erythematous rash over both lower extremities, fever, right inguinal adenopathy, and edema of the right foot and ankle. Following this episode the right lower extremity gradually enlarged, and intermittent bouts of

fever, chills, and vesiculopustular lesions on the enlarged limb occurred. From December, 1944, through April, 1951, she was hospitalized on six occasions because of recurrent cellulitis and vesiculopustular lesions on the extremity, or for Kondoleon operations on the leg. The latter were essentially unsuccessful.

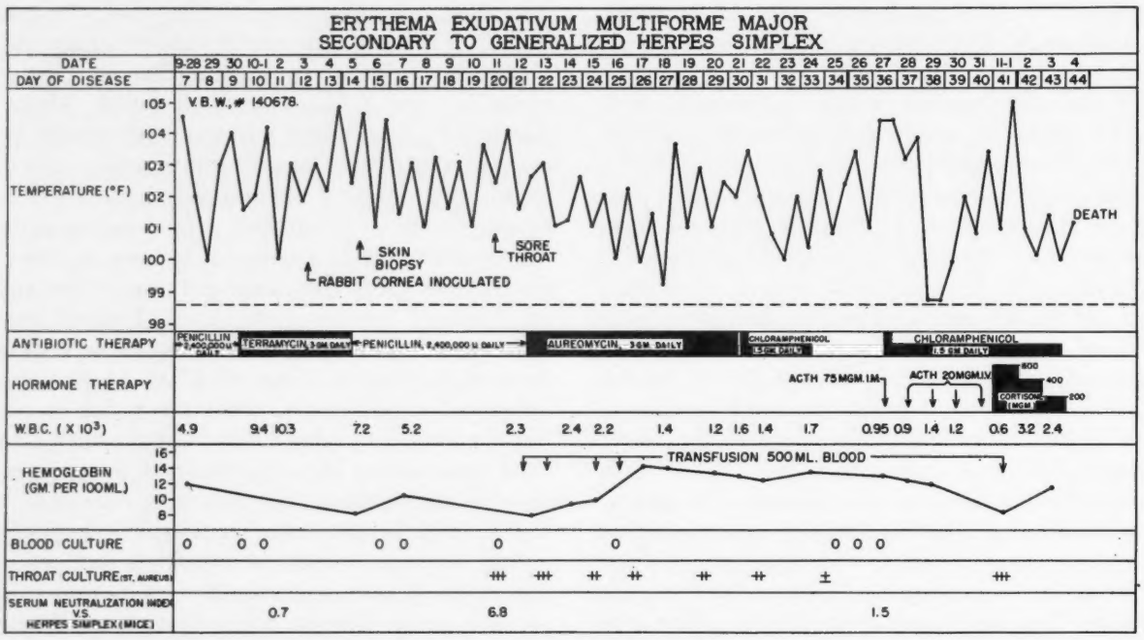

FIG. 1. Clinical course of patient V. B. W. Neutralization indexes of the patient's serum, as recorded in the chart, are in error. The corrected values appear in Table 1.

On September 20, 1951, at the onset of a menstrual period, she developed a vesicle on the right labium minus and an enlarged, tender lymph node in the right groin. Fever, chills and generalized myalgia ensued. She was admitted to the hospital on September 28th, acutely ill. Careful questioning failed to elicit any history of previous herpes labialis or other manifestations of herpetic infection, with the possible exception of the recurrent pustular lesions on the right lower extremity.

Physical examination revealed the following: The temperature was 104.6°F., respiratory rate 20, pulse rate 125 and blood pressure 100/70 mm. Hg. She was thin, poorly nourished, mildly disoriented and seemed acutely ill. No conjunctivitis was noted. There were two small vesicles at the angle of the mouth and several small, shallow ulcers on the buccal mucosa. Grouped vesicles, measuring 3 to 4 mm. in diameter, were present on both labia majora, and a crusted ulcer, 1 cm. in diameter, on the right labium minus. Single vesicles of the same character were present elsewhere on the perineum. The right leg was twice the size of the left as the result of firm, non-pitting edema. The skin was somewhat thickened but showed no lesions. A paronychia, draining purulent material, was present on the right great toe. The right inguinal nodes were slightly enlarged and tender.

Laboratory data were as follows: The urine showed no abnormality and was sterile on culture. The red blood cell count was 3.92 million per cu. mm., the hemoglobin 12.0 gm. per 100 ml., and the packed cell volume 35 per cent. The sedimentation rate was normal. The leukocyte count was 4,950 per cu. mm., with 56 per cent segmented neutrophils, 7 per cent stabs, 35 per cent lymphocytes and 2 per cent monocytes. Platelets were abundant in the blood smear.

The blood sugar, total serum proteins and A/G ratio, non-protein nitrogen and carbon dioxide combining power were within normal limits. The serum chloride value was 95.1 mEq. per L. A roentgenogram of the chest was normal. The electrocardiogram was considered abnormal because of low voltage and non-specific T-wave changes, and also was interpreted as suggesting right ventricular enlargement.

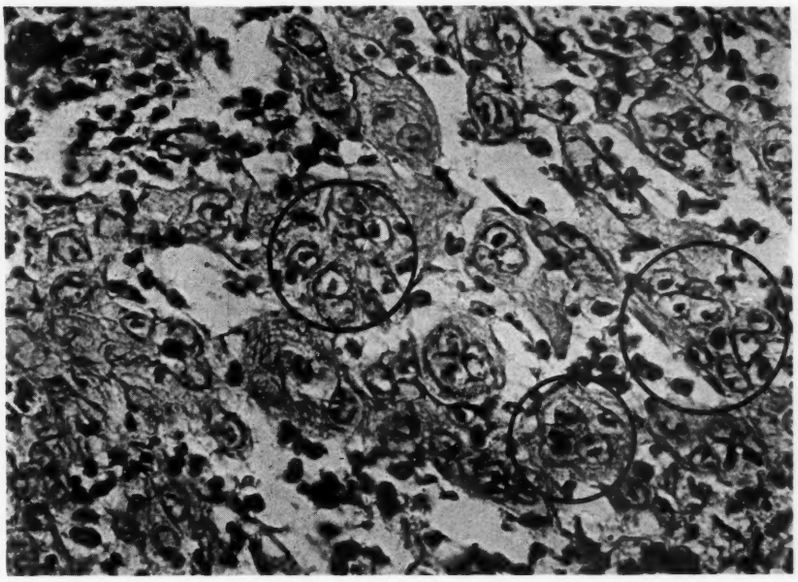

FIG. 2. Microscopic appearance of skin lesion. The squamous epithelium is infiltrated with leukocytes and cells are separated by fluid. The epithelial cells everywhere contain intranuclear inclusions, some prominent groups being noted within circles; hematoxylin and eosin, × 600.

A darkfield examination of material from the vulval ulcer showed no spirochetes, and serologic tests for syphilis (Wassermann, Kahn and VDRL) were repeatedly negative. The serum contained no agglutinins for sheep cells or for Brucella, typhoid or paratyphoid organisms. Cold hemagglutinins were repeatedly absent, and complement fixation tests with psittacosis and Q fever antigens gave titers of <1:8 in serum specimens obtained throughout her hospitalization. Repeated blood cultures were sterile. Material from the paronychia yielded Escherichia coli on culture and Staphylococcus albus was obtained from the vulval ulcer.

The patient's clinical course and the pertinent laboratory data are summarized in Figure 1. The mental confusion cleared but spiking fever continued during the administration of aqueous penicillin. The perineal lesions enlarged and the anterior surface of the right leg became inflamed. Scattered erythematous papules and groups of small, lentil-sized vesicles filled with clear fluid, resembling those on the perineum, appeared on the right leg and foot and on the right hand. Disseminated herpes simplex was suspected and materials were obtained for virus studies. Biopsy of the vesicle on the right forearm revealed many epithelial "balloon cells" with swollen nuclei containing marginated chromatin and acidophilic, type A inclusions. The tissue was infiltrated with round cells and a moderate number of polymorphonuclear leukocytes. (Fig. 2.)

Oral terramycin, substituted for penicillin, was likewise ineffective. Some skin lesions became bullous, measuring 1 to 2 cm. in diameter, and scattered new vesicles and bullae appeared over the trunk and extremities, as others became confluent, ruptured and crusted. (Figs. 3 and 4.) Although the vesicle fluid became cloudy, it contained no bacteria and no eosinophils were present. New lesions appeared in the mouth. Because of the changing character of the lesions and the severity of the illness, two consulting dermatologists classified the condition as a vesiculobullous type of erythema multiforme (EEM Major).

Further antibiotic therapy was carried out, not only in an effort to influence her general course but also to eradicate penicillin-resistant hemolytic Staphylococcus aureus which had appeared in the throat in association with an acute pharyngitis. These attempts were essentially unsuccessful. The skin lesions were drying with the formation of thick crusts.

She was discovered to have leukopenia and had become severely anemic. Whole blood transfusions were given with some benefit but the leukocyte count declined further. Because it was suspected that antibiotics might be contributing to the persistence of leukopenia, chloramphenicol therapy was discontinued tem-

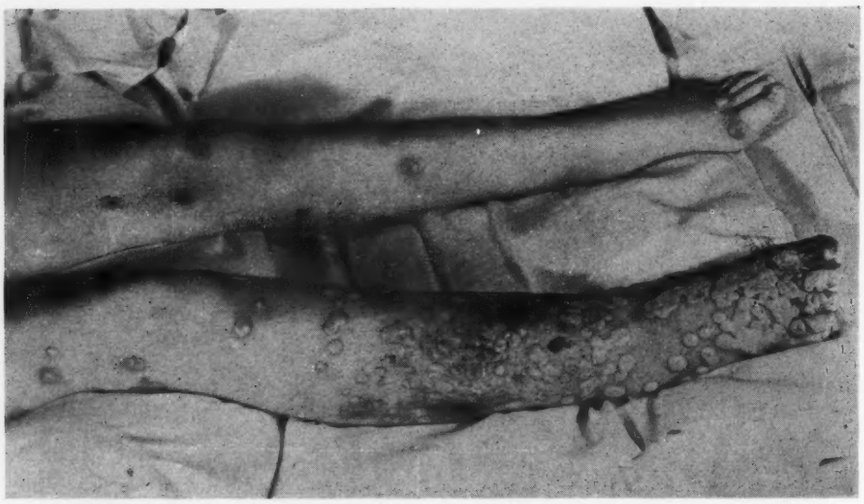

FIG. 3. The appearance of the bullous and vesicular lesions of the lower extremities on the nineteenth day of illness. The paronychia of the right great toe is also evident.

porarily, but was soon reinstated as pyrexia recurred.

Her general condition deteriorated rapidly. She appeared extremely ill, had dark, crusted lesions about the mouth, a weak cough productive of some mucoid sputum, and a tachycardia of 120 to 140 beats per minute with a gallop rhythm. Although lacking overt evidence of congestive cardiac failure, she was digitalized. ACTH had been withheld earlier in her illness because of its deleterious effect in some viral infections. Direct blood counts, however, showed 12 to 25 eosinophils per cu. mm. in the face of her high fever and acutely ill state, and her adrenocortical response was considered inadequate. Therefore, and because of its effectiveness in some reported cases of EEM Major,[54] she was given 20 mg. of ACTH by eight-hour intravenous infusion daily. She continued to do poorly and to have tachycardia. An initial, dramatic fall in temperature occurred on ACTH therapy; however, it rose again to 105°F. and she appeared moribund, developing abdominal distention, presacral and ankle edema, and increasing respiratory difficulty with signs of fluid in the pleural cavities. The latter necessitated oxygen administration. An EKG showed prolonged A-V conduction.

Her leukocyte count dropped to 600 cells, and total eosinophils numbered 12.5 per cu. mm. ACTH was discontinued, and she was transfused and given cortisone acetate, 600, 400 and 200 mg. on succeeding days. She complained of increasingly sore mouth, and a deep ulcer was discovered at the base of the tongue and on a tonsillar pillar. On cortisone therapy the leukocytes increased and her fever diminished. However, dyspnea worsened, the lungs filled with moist rales, and she became comatose, expiring quietly on November 3rd.

At necropsy,* in addition to the crusting lesions of the skin and eschar-covered excoriations about the nose and lips, an extensive ulcer covered with creamy exudate was present on the posterior aspect of the tongue. There were 100 to 150 ml. of serous fluid in the peritoneal and pericardial cavities. Both lungs were compressed by clear, serous pleural effusions measuring approximately 800 ml. each.

The *heart* weighed 250 gm. Three small patches of easily detachable, white exudate were present on the anterolateral surface of the left ventricle. The myocardium was very pale, and pale yellow, non-opaque areas, measuring up to 1 cm. in diameter, were present throughout the septal and left ventricular myocardium, which was of normal thickness. Both ventricular cavities were moderately dilated. The heart valves and the coronary arteries were normal. Microscopically an interstitial myocarditis was present, characterized by infiltration with macrophages, small round cells, and plasma cells and by considerable interstitial edema. No myocardial necrosis was evident. The right *lung* weighed 350 gm. and the left 300 gm. They were atelectatic and firm, only the anterolateral aspect of the lobes being crepitant. The cut surface of the lungs was quite dry, and trian-

* The autopsy (No. V-51-188) was performed by Dr. Marcus J. Zbar.

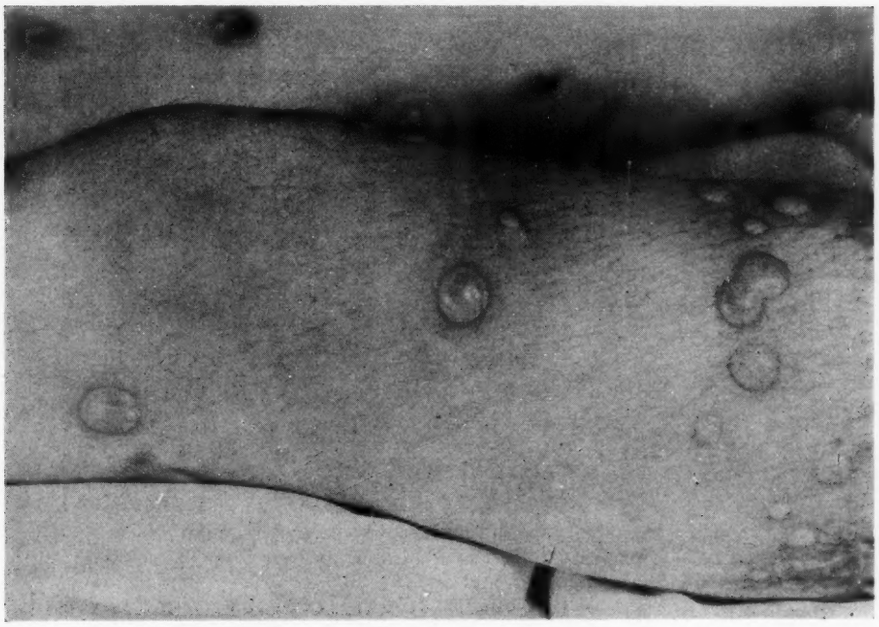

FIG. 4. Closer view of lesions on the right lower extremity. The bullous character is evident, and the dark crusts of ruptured lesions appear on the left leg.

gular, purplish-red areas were present throughout, those more deeply located being spherical. Some were firmer, elevated and grayish-pink in color. Microscopically the appearance of the lungs varied in conformity with the grossly visible changes. A considerable amount of interstitial and intra-alveolar edema fluid, and an interstitial infiltrate of round cells and macrophages was generally present. The main alteration, corresponding to the circumscribed areas seen grossly, was an organizing fibrinous pneumonia, macrophages comprising the main cellular element of the exudate. Few, if any, polymorphonuclear leukocytes were present. In the more central zones organization of the exudate, accompanied by proliferation of fibroblasts, was evident. The severity of these pneumonic changes varied in different locations. In addition, small, circumscribed areas of necrosis were present. A careful search in areas of the most recent pneumonitis failed to reveal intracellular inclusions. The *bronchial radicles* grossly were filled with tannish, tenacious mucus, and the mucosa was inflamed and hyperemic. Microscopically no significant changes were noted in the bronchi. The *esophagus* in its middle third contained three small ulcers, the largest measuring 1.5 cm. No inclusions were seen microscopically. The areas of ulceration penetrated through the mucosa into the underlying muscle layer. Interstitial edema and infiltration with round cells was present.

The *liver* weighed 1,850 gm. and appeared light red-brown in color with areas of purplish congestion. On section the parenchyma appeared somewhat granular and mottled with small grayish-yellow areas and a few bright red, pinpoint-sized hemorrhages. Microscopically there were numerous, small areas of focal necrosis without evidence of cellular inclusions. Some were hemorrhagic. The portal areas contained slight to moderate round cell infiltration. The *spleen* weighed 200 gm. and was soft and flabby, with scattered dark purple areas of infarction, thrombi being evident microscopically in some of the smaller veins. In other areas innumerable minute areas of necrosis were present. The *adrenals* were enlarged 1.5 to 2 times normal size. Microscopically a few tiny areas of recent necrosis were present in the cortices. The right *kidney* weighed 160 and the left 180 gm. The cortices were congested, and scattered, opaque, triangular infarcts, measuring 3 to 5 mm., were present on section. The kidneys were not otherwise remarkable. Microscopically interstitial edema and areas of necrosis corresponding to the grossly visible infarcts were present. Thrombosis of small arteries was demonstrable in relation to several of these infarcts.

The *bone marrow* microscopically revealed a

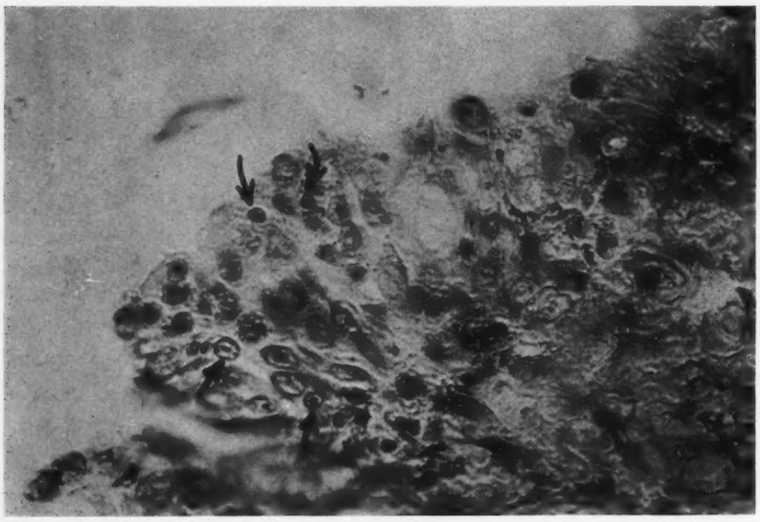

FIG. 5. Nictitating membrane of rabbit seventy-two hours following inoculation of eye with vesicle fluid from patient; intranuclear herpetic inclusions in epithelial cells; hematoxylin and eosin, × 300.

severe hypoplasia of all hematopoietic elements, presenting in some areas an almost aplastic appearance. Megakaryocytes were least reduced of all the cellular elements. The *skin* showed changes varying from ulceration down to the subcutaneous fat to regeneration of the epidermis beneath dense fibrinous eschars some of which contained bacterial colonies. The corium was infiltrated with inflammatory cells. No evidence of inclusions was found in a careful search of many sections of cutaneous epithelium. The remainder of the autopsy examination, including that of the central nervous system, disclosed no significant abnormalities.

Culture of the lungs and other organs, both for bacteria and fungi, yielded no significant pathogenic micro-organisms.

Final anatomical diagnoses were: Hypoplasia of bone marrow of undetermined cause; organizing fibrinous pneumonia of undetermined etiology; interstitial myocarditis of undetermined etiology; infarcts of kidney and spleen; minimal hydroperitoneum and hydropericardium; massive, bilateral hydrothorax with pulmonary atelectasis.

EXPERIMENTAL

Isolation and Identification of Herpes Simplex Virus

1. *Rabbits.* The scarified cornea of a rabbit was inoculated with material obtained from a ruptured vulval vesicle on the twelfth day of the patient's illness. Typical herpetic keratoconjunctivitis had developed within twenty-four hours. Histologic sections of the nictitating membrane removed at seventy-two hours showed herpetic inclusions in the epithelial cells. (Fig. 5.) Suspensions of the membrane* were transferred to a second rabbit which likewise developed severe keratoconjunctivitis. The first rabbit developed evidence of encephalitis from which it recovered. On the 119th day following the initial inoculation of the eye the rabbit was given an intracerebral challenge with a known strain of herpes simplex virus† in the form of 0.1 ml. of a 20 per cent suspension of infected mouse brain. No reaction or illness ensued. Neutralizing antibody for herpes virus in the rabbit's serum was not determined prior to the challenge.

Material obtained on the same date from a vesicle on the patient's lower extremity likewise produced typical herpetic keratoconjunctivitis when inoculated onto the scarified rabbit cornea.

2. *Embryonated Eggs.* Materials from the patient which were used for inoculation of the rabbit cornea and, in other experiments, material from the eye of rabbits with kerato-

* All passage materials were cultured in Brewer's thioglycollate medium or on blood agar plates. Penicillin and streptomycin were added to prevent bacterial contamination.

† Originally isolated by Dr. J. T. Syverton and furnished by Dr. William F. Scherer, University of Minnesota, as infected mouse brain in 50 per cent glycerol. Third passage material in mice had an LD_{50} of 4.8.

conjunctivitis were suspended in sterile isotonic saline containing penicillin and streptomycin and were inoculated onto the dropped chorioallantois of embryonated hen's eggs of twelve days' incubation. Typical herpetic plaques, showing ectodermal proliferation with a few intranuclear inclusions, were produced in approximately one-half of the eggs through two passages. In additional passages unequivocal lesions were not produced and attempts to recover the virus from the original materials by inoculation of eggs and mice failed. The original and passage materials had been stored at −40°C. as saline suspensions for as long as three to four weeks in some cases. The instability of herpes virus, especially as egg membrane material, frozen in normal saline is well known.[44]

Repeated attempts by inoculation of embryonated eggs, mice and guinea pigs to isolate a virus from the pulmonary and cutaneous tissues obtained at necropsy were unsuccessful.

Examination of Patient's Serum for Herpes Neutralizing Antibody

Sera were obtained from the patient on the eleventh, twentieth and thirty-sixth days of illness and were frozen at −40°C. until tests for neutralizing antibody were carried out in mice on May 3, 1952.

The sera were inactivated at 56°C. for thirty minutes prior to the tests. The virus used consisted of the previously mentioned 20 per cent suspension of infected mouse brain. Using phosphate-buffered saline, pH 7.4, decimal dilutions of virus were prepared, and 0.25 ml. quantities were mixed with equal volumes of the patient's inactivated sera. Similar mixtures of viral dilutions and inactivated normal rabbit serum served as a control. Final virus dilutions of 10^{-2} to 10^{-6} were obtained. The mixtures were incubated at 37°C. for two hours following which 0.03 ml. quantities were injected intracerebrally into lightly anesthetized white Swiss mice weighing 10 to 15 gm. Deaths occurring within forty-eight hours were considered traumatic and these animals were discarded.

During the twenty-one-day period of observation those animals dying of encephalomyelitis were noted, and 50 per cent mortality end points were calculated by the formula of Reed and Muench.[37] Neutralization indexes were computed, as described by Paul,[35] by a comparison of the LD_{50} of the control serum with that obtained with each serum specimen from the patient. The results appear in Table 1. With the strain of herpes used, insignificant quantities of neutralizing antibody were present in the initial specimen, and the neutralization index increased to a just significant value during the course of her illness. However, similar determinations of neutralizing antibody using the HF strain of herpes virus, which were carried out elsewhere,* showed indexes of >33,000 for the first, >36,000 for the second and >63,000 for the third serum specimens.

TABLE 1
DETERMINATION OF NEUTRALIZING ANTIBODY FOR HERPES SIMPLEX IN PATIENT'S SERUM

Serum Specimen	Dilution of Virus					LD_{50}	Neutralization Index
	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}		
Control*	6/6†	6/6	4/4	0/5	0/5	4.5	....
10/2/51	5/5	2/4	2/5	1/6	1/4	3.8	5.0
10/11/51	5/6	2/5	0/5	0/5	1/4	2.8	50.1
10/27/51	3/3	3/5	1/6	0/6	1/4	3.4	12.6

* Normal rabbit serum.
† Number dying/total number inoculated.

COMMENTS

The data obtained in the study of this patient —the demonstration of intranuclear inclusions in the skin lesions; the production of keratoconjunctivitis and encephalitis in rabbits with material from the lesions of two separate sites, the presence of intranuclear inclusions in the nictitating membranes of these animals, and their subsequent immunity to an intracerebral challenge with a known strain of herpes simplex virus; the production of plaques on the chorioallantois of embryonated eggs with virus-containing materials; and the patient's development of increasing serum antibody titer against two strains of herpes simplex virus—represent strong evidence in favor of an infection with herpes simplex virus, probably primary in nature. Lesions observed early in the course of the illness appeared typically herpetiform; however, their character distinctly changed as a clinical state indistinguishable from EEM Major developed. The failure to isolate herpes virus from the tissues

* Virus and Rickettsia Section, Communicable Disease Center, U. S. Public Health Service, Montgomery, Ala., through the courtesy of Dr. Morris Schaeffer, Director.

obtained at necropsy is not surprising in view of the duration of the patient's illness.

The disseminated herpetic lesions correspond to those of Kaposi's varicelliform eruption as seen in adults. This disease, it now seems well established, results from infection either with the virus of herpes simplex or that of vaccinia, the former being responsible in approximately 75 to 80 per cent of instances. Most reported cases have occurred in children with chronic dermatoses which appear to facilitate viral infection of the skin. These cases may often represent the primary infection with herpes virus.

Primary infections with herpes simplex occur and are demonstrated uncommonly in the adult. Of the twenty-four acceptable instances collected by Kilbourne and Horsfall[26] in a recent review, only two[27,42] took the form of Kaposi's eruption. Blattner et al.[9] and Buerk and Blank[12] have each described an additional case. In these instances an increase in herpetic antibody titer was demonstrated in the serum during convalescence. Burnet and Williams[14] and others have demonstrated in infants and children with the usual manifestation of primary herpetic infection, acute gingivostomatitis, that specific neutralizing antibody appears in the serum during the course of the infection, and this feature has been emphasized as being essential to the diagnosis of primary infections.[26]

Only a few cases of Kaposi's eruption have occurred in individuals subject to recurrent herpes simplex.[10,32] It seems very unlikely that this patient had a recurrent infection which became disseminated, since no history of previous herpetic lesions was obtained upon careful questioning. Recurrent herpes has been considered to result from activation of virus persisting in the tissues following the initial infection, rather than from newly acquired, repeated infections.[14] This persistence of virus in the tissues following the initial rise in antibody in response to the primary infection presumably accounts for the measurable quantities of antibody ordinarily demonstrable in the serum during the remainder of life.[5,13,22,41]

The differences in the degree of neutralization exhibited by the same serum specimens against the two strains of herpes virus are difficult to explain, unless serologic differences in strains are involved. These serologic differences are regarded as questionable at present, although some investigators have purported to demonstrate them. The neutralizing titer of her serum increased against both strains of herpes virus during the course of her illness, as would be expected in a primary herpetic infection. The rather high titer of the initial specimen against the HF strain of herpes may possibly be a result of the specimen's having been obtained as late as the eleventh day of illness.

Although *post hoc* reasoning may lead to erroneous conclusions, it is difficult to avoid the belief that the development of EEM Major was causally related to the disseminated herpetic infection which immediately preceded it in the case described here. Additional efforts to isolate viral agents from these cases should be made, with emphasis upon the dermatropic group, since these seem most clearly implicated at this time. In view of the fact that EEM Major is an unusual occurrence whatever the precipitating agent, it seems unlikely that studies made in the opposite direction, e.g., the frequency of the development of EEM in individuals with herpetic infections, will be illuminating.

SUMMARY

Information concerning the relationship of viral agents to the development of erythema exudativum multiforme major (Stevens-Johnson syndrome) and minor (Hebra type) has been briefly summarized and discussed. Most attempted virus isolations have been unsuccessful or have yielded inconclusive results. Both on clinical grounds and on the basis of previously reported studies there is reason to believe that herpes simplex virus may be implicated in the pathogenesis of at least some instances of the disease.

A case of EEM Major is presented in which disseminated herpes simplex seemed to be the precipitating factor. The virologic and serologic studies related to this case have been described.

Addendum: Since this paper was submitted for publication, Sezer (*Am. J. Ophth.*, 36: 301, 1951) has reported the isolation of a presumably previously unrecognized virus from three patients with Behçet's syndrome. Although the studies on these three apparently identical viral strains were not exhaustive, certain cultural and serologic characteristics were examined and it was concluded that the organism was unrelated to the viruses of herpes simplex,

lymphocytic choriomeningitis or Theiler's mouse encephalomyelitis.

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Determination of C-reactive Protein in Serum As a Guide to the Treatment and Management of Rheumatic Fever*

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In response to a variety of inflammatory stimuli there appears in the blood of human beings a protein, not normally present, which may be identified by its capacity to form a precipitate with the somatic C-polysaccharide of the pneumococcus.[1] It has therefore been named "C-reactive protein" (CRP).[2] Minute amounts of this protein may be demonstrated in human serum by a precipitin test employing a specific antiserum obtained from rabbits hyperimmunized by repeated injections of purified C-reactive protein.[3,4] In previous studies it has been demonstrated that the appearance of C-reactive protein in the blood is a non-specific but extremely sensitive indicator of the presence of an inflammatory reaction.[4] In 1950 Anderson and McCarty[5] demonstrated the usefulness of this test for the detection of low-grade inflammation in patients with rheumatic fever. More recently Ziegra and Kuttner[6] and Bunim and his associates[7] have observed the behavior of CRP in the serum of patients treated with antirheumatic agents.

The present study adds observations on sixty-two patients in whom serum C-reactive protein determinations were carried out during various stages of rheumatic fever. The usefulness of this test for the detection of rheumatic activity is demonstrated, and certain limitations emphasized.

MATERIALS AND METHODS

The patients included in this study were admitted to Irvington House in the acute, chronic or convalescent stages of rheumatic fever. They were observed until all evidence of the disease had subsided and through a convalescent period of approximately six months thereafter. At weekly intervals during the acute stage of the disease, and monthly during convalescence, blood samples were obtained for serologic tests, erythrocyte sedimentation determinations and white blood cell counts. Electrocardiograms and teleroentgenograms were obtained at similar intervals. Sera were frozen and stored at −20°C. until used. Most patients were treated with either cortisone, ACTH or acetylsalicylic acid. The dosage of these was varied freely in most instances according to the clinical response of the patient. In general, treatment was initiated with daily doses of either 300 mg. of cortisone, administered orally or intramuscularly, 120 mg. of ACTH, or 1 gr. of acetylsalicylic acid per pound of body weight. The dose thereafter was gradually reduced and treatment was continued for a minimum period of six weeks. Three patients were given aminopyrine in daily oral doses of ⅕ gr. per pound of body weight. Two patients received sodium gentisate in doses of from 12 to 16 gm. per day.

The test for C-reactive protein was performed by the capillary precipitin method as described by Anderson and McCarty[5] employing an antiserum prepared by injecting rabbits with purified, crystalline C-reactive protein of human origin.‡ Antistreptolysin O determinations were made by Rantz and Randall's modification[8] of

‡ The rabbit antiserum was generously supplied by Drs. Maclyn McCarty and Harrison Wood of the Hospital of the Rockefeller Institute.

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the original method of Todd.[9] The erythrocyte sedimentation rate (ESR) was determined by the Wintrobe method and corrected for variations in hematocrit according to standard tables.

All of the patients included in this study met the criteria of Jones[10] for the diagnosis of rheumatic fever at some time during the course of their disease. Patients were grouped as follows:

Group I: This group consisted of those patients observed during a period of *frank rheumatic activity*, indicated by the simultaneous presence of at least one major manifestation (carditis, polyarthritis, subcutaneous nodules or chorea) and two minor manifestations (fever, elevated erythrocyte sedimentation rate, erythema marginatum, prolongation of the P-R interval or other abnormal electrocardiographic changes) or by the presence of two major manifestations. Thirty-five patients were included in this group.

Group II: This group consisted of those patients observed with definite *low-grade rheumatic activity* as evidenced by the simultaneous presence, following a frank rheumatic attack, of at least two of the following three minor manifestations: fever (at least 100.3°F. rectally), elevation of the erythrocyte sedimentation rate to 15 mm. per hour or greater, prolongation of the P-R interval to 0.04 seconds beyond the values listed for various ages and cardiac rates in the tables of Ashman and Hull.[11] Eleven patients were included in this group. One of these, who did not meet the criteria listed, was included because of persistent tachycardia and marked limitation of cardiac reserve which was interpreted as persistent carditis despite the absence of fever or elevation of ESR.

Group III: This group was composed of eleven patients recently recovered from a frank attack of rheumatic fever in whom the diagnosis of continued rheumatic activity was in doubt. Ten of these patients had persistent elevation of ESR and the significance of this finding with regard to the persistence of the active rheumatic process was difficult to assess. The remaining patient had subcutaneous nodules (confirmed by biopsy as typical of rheumatic fever) as an isolated manifestation without any other clinical or laboratory finding to suggest rheumatic activity.

Group IV: This group consisted of patients with so-called "pure" chorea as an isolated manifestation unassociated with any of the minor manifestations listed above. Five patients were included in this group.

RESULTS

Correlation of the Test for CRP with Rheumatic Activity (*Table I*). C-reactive protein was present in moderate to large amounts in the sera of all but one of the thirty-five patients studied when the manifestations of frank rheumatic activity were present. The typical behavior of CRP in the serum of a patient with frank rheumatic activity is illustrated (Fig. 1) by the first case report (Case I, D. G.). The only patient in this group in whom the test for CRP was negative had Sydenham's chorea, slight elevation of the sedimentation rate and soft apical and basal systolic murmurs of possible significance. Despite the clinically apparent low-grade nature of the rheumatic process he was classified as having frank rheumatic activity on the basis of the criteria established for the study.

TABLE I

RELATIONSHIP OF THE STAGE OF RHEUMATIC ACTIVITY TO THE PRESENCE OF C-REACTIVE PROTEIN (CRP) IN THE BLOOD OF PATIENTS WITH RHEUMATIC FEVER

Rheumatic Activity	No. of Patients	CRP Positive	CRP Negative
Frank	35	34	1
Low-grade	11	10	1
Doubtful	11	6	5
"Pure" chorea	5	0	5

Of eleven patients studied during the stage of low-grade rheumatic activity following a frank attack of rheumatic fever, ten were found to have CRP present in their sera. The behavior of CRP in the serum of a patient with low-grade rheumatic activity is illustrated (Fig. 2) by the second case report (Case II, J. E.). The exception in whom the test was negative was a patient who did not strictly meet the defined criteria. Following a prolonged and severe bout of congestive heart failure this patient had neither elevation of the sedimentation rate, fever nor heart block but because of persistent tachycardia and marked limitation of cardiac reserve was considered to have low-grade carditis and therefore was included in the group of patients with low-grade activity.

The third group consisted of eleven patients in whom there was doubt as to whether the acute rheumatic process had subsided, usually because of persistence of elevation of the erythrocyte sedimentation rate. Of this group the test

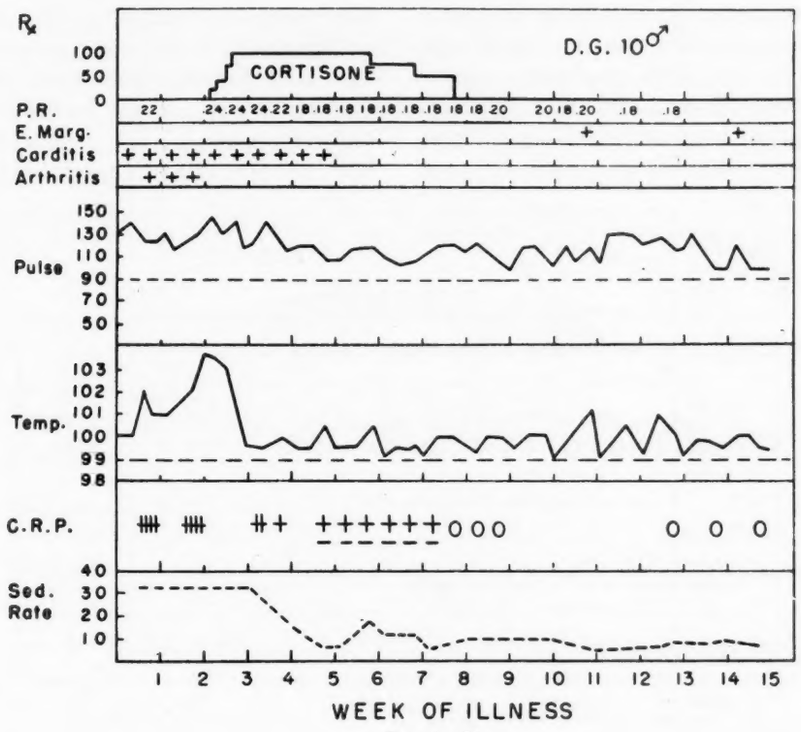

FIG. 1. Case I.

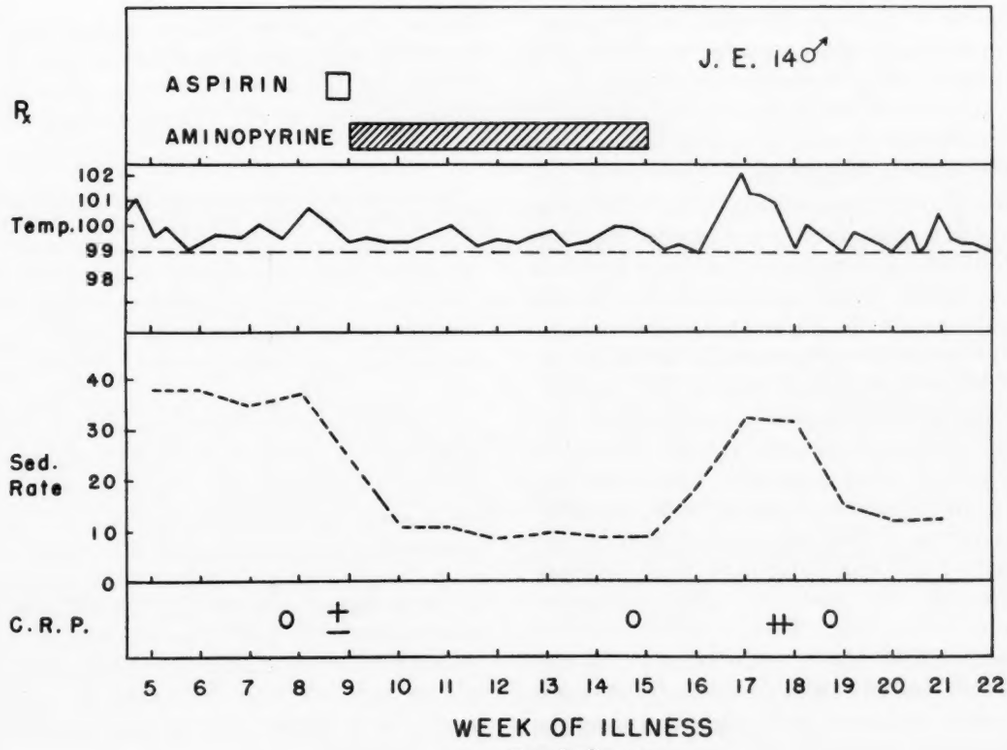

FIG. 2. Case II.

for CRP was positive in six and treatment was initiated. In the remaining five in whom the test was negative, the ESR gradually fell to normal levels spontaneously and these patients subsequently had an uneventful recovery. Case III (M. G.) serves as an illustration of the particular value of the test for CRP in providing objective evidence of low-grade rheumatic inflammation in this group of patients. (Fig. 3.)

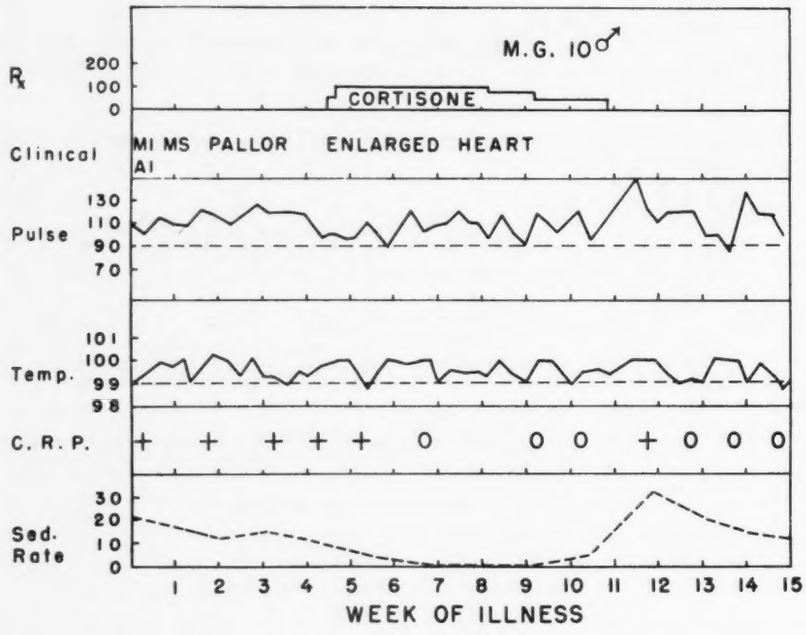

FIG. 3. Case III.

Five patients in this series had so-called "pure" chorea unassociated with any other clinical or laboratory finding suggestive of rheumatic activity. In all five of these the test for CRP was negative. CRP was also absent from the cerebrospinal fluid obtained from three of these patients during the peak of choreiform activity. Of six other patients who had chorea associated with other manifestations of rheumatic activity, the test for CRP was positive in four. Of the remaining two in this category one was included in the group having frank rheumatic activity (Group I) and has already been discussed. The remaining patient requires special mention since, in addition to chorea, he had erythema marginatum, and when both manifestations were present simultaneously the test for CRP remained negative.

Behavior of CRP during Antirheumatic Therapy (*Table II*). Twenty-three patients who were treated with cortisone and four who received ACTH showed a reversal of the test for CRP from positive to negative. This usually occurred within the first week of treatment. One patient with severe pancarditis, however, continued to manifest a positive test for CRP while receiving daily doses of 300 mg. of cortisone during the first few weeks of treatment and despite gradual clinical improvement. CRP disappeared from his serum when the dose of cortisone was raised to 400 mg. per day. In several other instances during the course of hormone therapy attempts to lower dosage too rapidly resulted in prompt reappearance of CRP in the patient's serum before any other clinical or laboratory sign of relapse was evident. The test for CRP thus served as a sensitive indicator of suppression of the inflammatory process.

TABLE II

BEHAVIOR OF C-REACTIVE PROTEIN IN THE BLOOD OF PATIENTS WITH RHEUMATIC FEVER DURING AND AFTER ANTIRHEUMATIC THERAPY

Antirheumatic Agent	No. of Patients Treated	CRP Disappeared during Therapy in	CRP Reappeared after Therapy in	No. Retreated
Cortisone	23	23	12	5
ACTH	4	4	4	0
Aspirin	26	19	6	3
Aminopyrine	3	2	1	0
Sodium gentisate	2	0	..	..

Of the patients treated with acetylsalicylic acid, in several instances it was not possible to reverse the positive test for CRP despite administration of the maximum dose that the patient could tolerate. In these patients substitution of cortisone therapy in the usual doses resulted in prompt clinical response and disappearance of CRP from the patient's serum. (Fig. 4, Case IV, J. C.) In general, however, CRP disappeared from the blood of most patients treated with acetylsalicylic acid as clinical manifestations of the disease were suppressed and as the ESR returned to normal.

A negative test for CRP during therapy did not necessarily indicate termination of the rheumatic process. A high proportion of patients in each treatment group showed symptoms, signs or laboratory evidence of relapse ("rebound") when administration of the antirheumatic agent was stopped. (Table II.) In most instances, however, the transient nature of the relapse was reflected in the spontaneous disappearance of CRP from the serum within two weeks. When the CRP remained in the blood for longer periods, it was considered evidence of persistence of the acute rheumatic process and treatment was reinstituted.

Manifestations and Stages of Rheumatic Activity Which May Be Associated with a Negative Test for CRP (Table III). Five patients with pure chorea in whom the test for CRP was negative have already been discussed. Erythema marginatum, like chorea, was associated with a negative test for CRP when it occurred as an isolated manifestation of the rheumatic process or when it occurred with chorea. It was observed in three patients in this series. One patient had typical

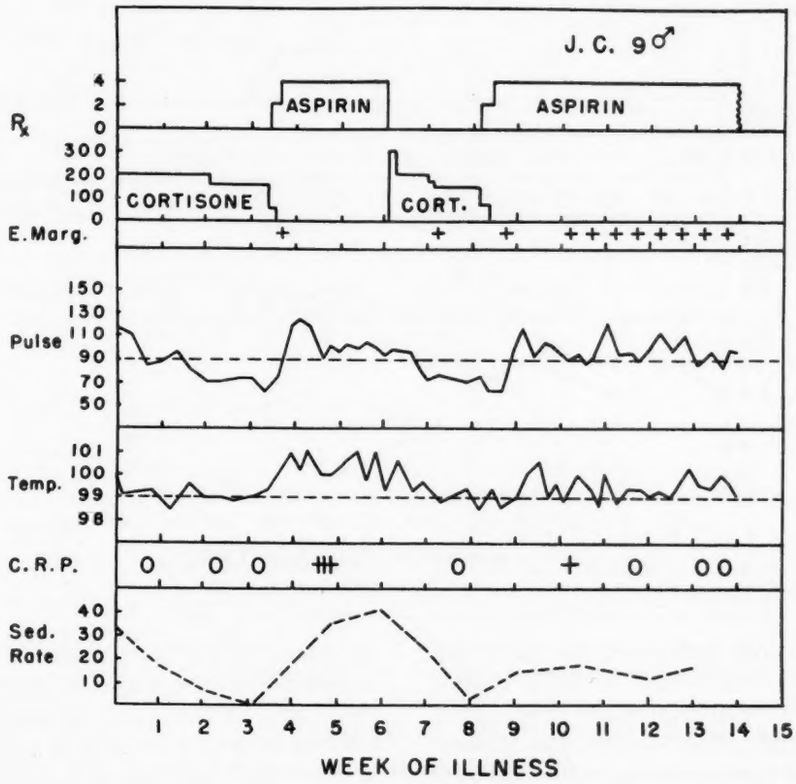

FIG. 4. Case IV.

TABLE III

ISOLATED RHEUMATIC MANIFESTATIONS AND STAGES OF RHEUMATIC FEVER WHICH MAY BE ASSOCIATED WITH A NEGATIVE TEST FOR C-REACTIVE PROTEIN

Manifestations or Stages of Disease	No. of Patients Studied
Chorea	5
Erythema marginatum	3
Subcutaneous nodules	1
Aschoff bodies in auricular appendage	1
Prolongation of P-R interval	1
Between polycyclic attacks	1
The latent period (phase II)	1

rheumatic subcutaneous nodules* at a stage of the disease when no other clinical or laboratory signs of active rheumatic fever were present. CRP was consistently absent from this patient's serum even during the period when new nodules were forming. Another patient in whom mitral commissurotomy was performed for the relief of mitral stenosis was found to have typical Aschoff nodules in the myocardium of the amputated auricular appendage despite the absence of CRP from his serum preoperatively. CRP was absent from the serum of a patient in the asymptomatic interval between two cycles of a polycyclic rheumatic attack. (Case v, J. M., Fig. 5.) It also failed to appear in the blood of another patient in the interval between an attack of Group A streptococcal tonsillitis and the onset of rheumatic fever.

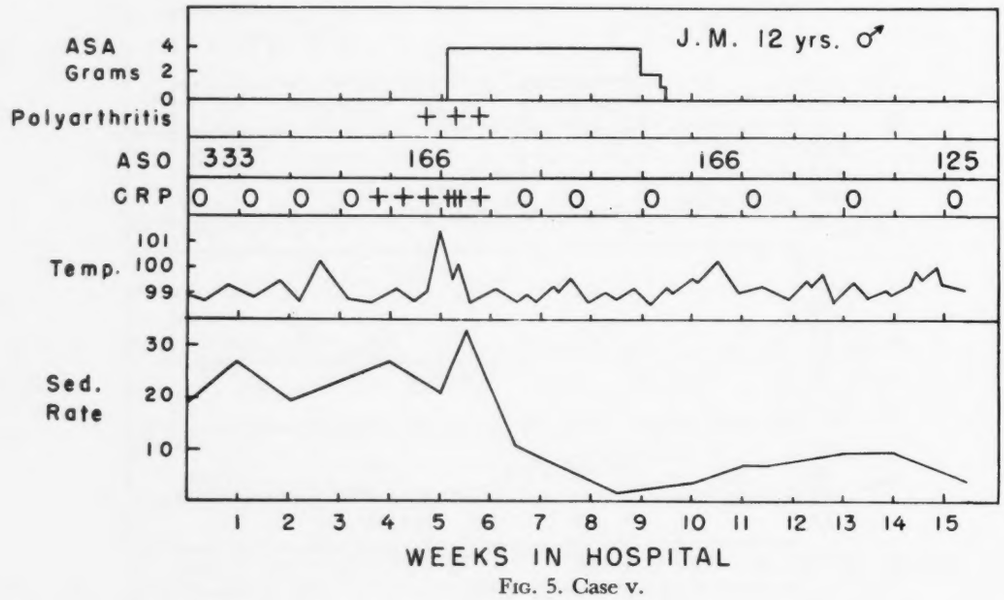

FIG. 5. Case v.

This group of patients indicates that various manifestations and stages of the rheumatic process may be so low-grade as to be below the threshold of an inflammatory stimulus necessary to cause the appearance of CRP in the blood and that despite the sensitivity of this test as an indicator of inflammation, a negative test for CRP does not necessarily exclude the concomitant presence of the rheumatic process.

CRP in the Serum of Patients with Chronic Rheumatic Carditis. Although the data presented above indicate that a negative test for CRP does not exclude the presence of rheumatic activity, a consistently positive test for CRP in the patient with rheumatic heart disease usually provides reliable objective evidence of the persistence of active carditis if other unrelated causes of inflammation can be excluded. Five patients in this series who had evidence of severe, protracted rheumatic carditis had detectable amounts of CRP in their sera for periods of from six months to more than one year with the exception of the intervals during which suppressive therapy with hormones or with salicylates was maintained (in some instances suppressive treatment was administered continuously for more than six months). In the presence of congestive failure the ESR may be depressed to normal values, despite the presence of frank rheumatic activity. Under these circumstances the CRP test usually remains positive unless it is reversed by treatment with antirheumatic agents. In the latter situation, congestive heart failure may persist despite reversal of the test for CRP to negative. However, in such instances CRP reappears upon withdrawal of the antirheumatic agent. It is thus evident that reversal of the CRP during treatment does not always indicate complete suppression of the active carditis. Case VI, B. T., (Fig. 6) illustrates the behavior of CRP in the blood of a patient with severe rheumatic carditis and congestive heart failure in whom the ESR was depressed to low values.

* Microscopic studies of the biopsied nodules were made by Dr. Leon Sokoloff.

CASE REPORTS

CASE I. D. G., a ten year old boy, was taken ill with anorexia, malaise and fever of 102°F. (Fig. 1.) He developed pain and tenderness over the dorsum of the right foot and a generalized macular eruption was noted on several occasions. On examination the pulse rate was 140, there was an apical diastolic gallop and a harsh apical systolic murmur developed which increased in intensity during this period of observation. An ECG revealed first degree A-V block. The ESR was 108 mm./hr. (Westergren). The patient was then admitted to Irvington House in the third week of his illness. On examination he appeared acutely ill. His temperature was 103.5°F. The right knee and left wrist were red, swollen and painful. The heart was enlarged and systolic and diastolic murmurs were heard at the apex. At this time the ESR was elevated and the test for CRP was strongly positive. When cortisone therapy was instituted, the acute manifestations of the disease were promptly suppressed. The response to therapy was characterized by disappearance of fever and polyarthritis and a fall to normal of the previously elevated sedimentation rate. However, there was a more gradual disappearance of the C-reactive protein. Traces of CRP persisted for several weeks as the only manifestation of the active disease but eventually disappeared before cortisone treatment was terminated. Following cortisone therapy, erythema marginatum appeared despite the absence of CRP from the patient's serum. The ESR remained normal.

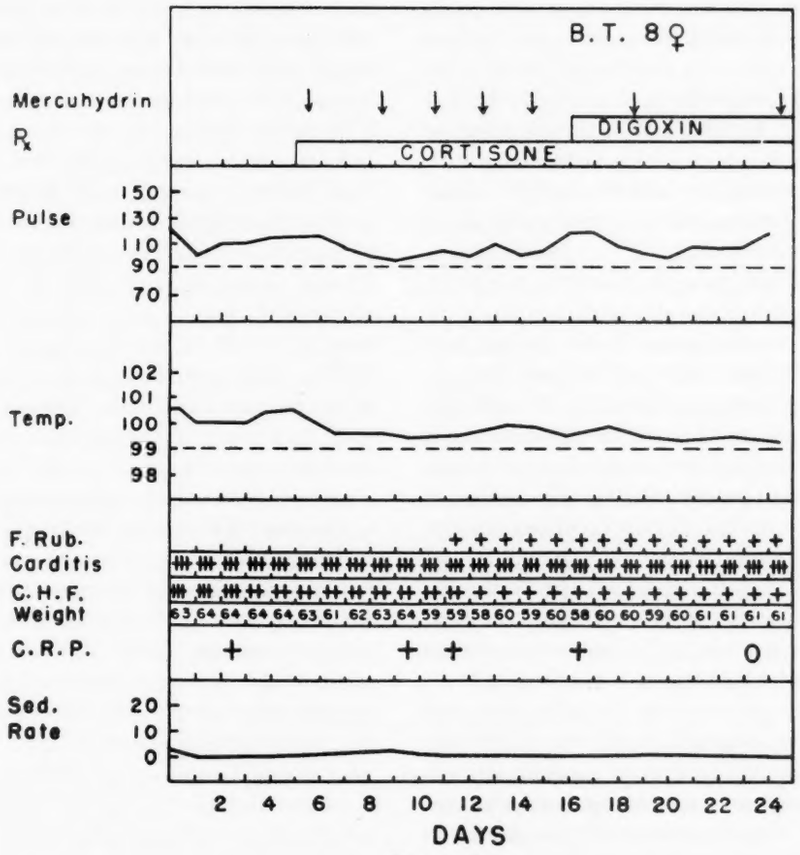

FIG. 6. Case VI.

Comment: This case illustrates the typical behavior of CRP in the serum of a patient with frank rheumatic fever before, during and after antirheumatic therapy. The persistence of even traces of CRP during antirheumatic therapy may be interpreted as evidence of active inflammation and in such instances therapy should be intensified or prolonged until CRP disappears completely.

CASE II. J. E. was a fourteen year old boy who at the age of nine had an illness characterized by fever, migratory polyarthritis and the

development of heart murmurs. Three months prior to admission he developed a sore throat and one week later became acutely ill with fever and severe chest pain. He was admitted to another hospital where a diagnosis of acute rheumatic fever was made. On examination a temperature of 102°F. was noted. The pulse rate was 140 per minute, the heart was enlarged, and systolic and diastolic murmurs were heard at the apex and base. An ESR was found to be 124 mm./hr. (Westergren) and the P-R interval was 0.22 seconds. A throat culture was positive for Group A streptococcus. He was treated with cortisone and penicillin and the acute manifestations rapidly subsided. Cortisone was withdrawn prematurely owing to the development of glycosuria and the patient promptly relapsed. He was re-treated successfully with aspirin.

On admission to Irvington House the patient was in no distress and had not received therapy for several weeks. He was found to be afebrile. The heart was enlarged and the physical signs of mitral insufficiency and stenosis and aortic insufficiency were present. His further course is illustrated in Figure 2. For several weeks the ESR remained elevated while the CRP, although originally absent from the patient's serum, became weakly positive. At times temperature elevations up to 101°F. were noted. He was treated with aspirin but was unable to tolerate effective doses and aminopyrine was substituted. This was followed by rapid disappearance of the fever and abnormal laboratory findings. After six weeks, therapy was stopped. There was transient reappearance of fever, CRP and elevation of ESR. This subsided spontaneously.

Comment: Continued low-grade rheumatic activity was diagnosed because of the elevated sedimentation rate, presence of fever and prolongation of P-R interval. The appearance of CRP in the serum established the significance of the other findings and pointed to the need for further treatment. The "rebound" phenomenon is well illustrated and substantiates the impression that the previously noted manifestations were those of rheumatic activity.

CASE III. M. G. was a ten year old boy with a past history of three attacks of Sydenham's chorea. (Fig. 3.) The onset of his present illness was insidious with a vague period of ill health characterized by frequent sore throat, fatigue and an indisposition to partake in his usual activities. A migratory polyarthralgia developed, along with low-grade fever, and a diagnosis of rheumatic fever was made. He was admitted to another hospital where both knees were found to be swollen and painful. The patient was febrile. The heart was enlarged and systolic and diastolic murmurs were heard at the apex. The ESR was 118 mm./hr. (Westergren). Treatment with ACTH was given with good response, following which he was transferred to Irvington House for further care. At this time examination revealed a pale, chronically ill-appearing boy. The heart was enlarged and the physical signs of mitral insufficiency, mitral stenosis and aortic insufficiency were found. During a period of observation no fever was noted but the ESR was elevated and there was persistent tachycardia. It was noted that during the period prior to treatment (Fig. 3) the CRP remained positive despite a fall in the previously elevated ESR. When cortisone was given, CRP disappeared from the patient's serum. Treatment was stopped and there was a "rebound," indicated by the transient appearance of CRP and elevation of ESR, both of which subsided spontaneously.

Comment: This case was classified as "doubtful" rheumatic activity because the sedimentation rate was transiently elevated in a patient with a recent history of rheumatic fever. A persistently positive test for CRP which could not be explained on any other basis indicated continuing rheumatic activity of low intensity. The response to treatment and the "rebound" when cortisone was stopped supported this impression.

CASE IV. G. C., a nine year old boy, was admitted to Irvington House in his third attack of rheumatic fever. For one month prior to the acute onset he appeared listless, complained of fatigue, and skin lesions typical of erythema marginatum were noted. Fever and polyarthritis developed and he was admitted to another hospital. At this time aspirin did not relieve his symptoms but he responded to 100 mg. of cortisone daily. After two weeks cortisone dosage was reduced to 75 mg. daily and he returned home. Two weeks later the acute process flared up again with severe carditis and the development of congestive heart failure. At this time a pericardial friction rub was heard. Cortisone dosage was increased to 200 mg. daily and improvement ensued. Ten days after the onset of this relapse he was admitted to Irvington House. The patient appeared pale and chronically ill but was in no acute distress. There was a heaving precordial systolic thrust, the

heart was enlarged, a loud systolic murmur was heard at the apex and a faint blowing diastolic murmur was audible at the left sternal border. The clinical course is shown in Figure 4. Cortisone was continued at 200 mg. daily with adequate suppression of rheumatic activity; but several weeks later when aspirin was substituted for cortisone, there was a prompt relapse with fever, tachycardia, elevation of ESR and the appearance of CRP in the patient's serum. These manifestations were controlled again with cortisone. When aspirin was substituted later on there was only a transient reappearance of CRP. He maintained his improvement when suppressive therapy was stopped. Erythema marginatum, which was present through all phases of his illness, continued to appear sporadically despite the absence of other clinical and laboratory evidence of rheumatic activity. Three months later he developed Sydenham's chorea. With this additional major manifestation and the simultaneous presence of erythema marginatum, the test for CRP and the ESR remained normal.

Comment: This case illustrates how C-reactive protein can be suppressed along with the other manifestations of rheumatic fever when treatment is adequate. Its reappearance during therapy would indicate that drug dosage should be increased or that a more potent antirheumatic agent should be employed. The failure of CRP to appear in the presence of frank chorea and erythema marginatum indicates that a negative test for CRP does not necessarily exclude persistence of the rheumatic process.

Case v. J. M. was a twelve year old boy with a past history of two episodes of acute rheumatic fever. His present illness began after two years had elapsed without evidence of rheumatic activity, and was characterized by fever, polyarthritis and carditis. He was treated with salicylates at another hospital and there was rapid subsidence of all clinical symptoms. Following completion of therapy he was transferred to Irvington House where no evidence of rheumatic activity was observed other than an elevated sedimentation rate. The heart was enlarged and the physical signs of mitral insufficiency and stenosis were present. The test for C-reactive protein was negative. It was decided to ambulate the patient despite the elevated ESR. Shortly thereafter he was seen limping about and complained of pain in the left hip. Fever developed and both knees became hot, swollen and painful. It is seen (Fig. 5) that CRP appeared in the patient's serum before fever and polyarthritis developed. He was treated with salicylates and there was rapid suppression of all clinical and laboratory findings.

Comment: This episode took place in a patient receiving penicillin prophylaxis and in whom no Group A streptococci could be demonstrated after repeated throat cultures. His antistreptolysin O titers showed a progressive fall during this period of observation and did not suggest a new streptococcal infection. The last episode of polyarthritis and fever was therefore regarded as another exacerbation of polycyclic rheumatic fever rather than a recurrence initiated by a new Group A streptococcal infection. Therefore the disappearance of CRP from the patient's serum does not always indicate termination of the rheumatic attack.

Case vi. B. T., an eight year old girl, had a past history of frequent sore throat for which her tonsils had been removed two years before. Since infancy periodic physical examinations had not revealed any evidence of heart disease or other ailment. In June, 1952, following an upper respiratory infection, she developed intermittent low-grade fever, anorexia, malaise and chronic fatigue. As her illness progressed cough and dyspnea made their appearance and a diagnosis of pneumonitis was made. Various antibiotics were given in succession without improvement. Her condition deteriorated further. The dyspnea increased, abdominal pain and distention appeared and peripheral edema became evident. At another hospital clinic the diagnosis of acute rheumatic fever, active carditis and congestive heart failure was made. Treatment with cortisone, digitalis, diuretics and salt restriction resulted in slight improvement. In October, 1952, she was admitted to Irvington House. On physical examination the patient appeared chronically ill, with marked wasting of the extremities and a protuberant abdomen. Dyspnea and orthopnea were not observed at rest but the neck veins were distended and pulsating. A firm, tender liver edge could be palpated below the level of the umbilicus and hepatic pulsation was marked. A hepatojugular reflux could be elicited. There was a diffuse precordial systolic heave and the heart was greatly enlarged. The heart sounds were of poor quality and at the apex grade IV systolic and low-pitched diastolic murmurs were heard. X-ray examination revealed a diffusely enlarged heart suggesting pericardial effusion, marked

cardiac dilatation or both. Her clinical course is charted in Figure 6. There was no fever or elevation of the ESR. The test for CRP was positive and became negative on cortisone therapy. Frequent injections of mercurial diuretics were given to control fluid retention and the patient gradually improved.

Comment: This case illustrates the insidious onset of rheumatic fever with severe carditis resulting in congestive heart failure. Under these circumstances the ESR may become normal and no longer parallel the degree of rheumatic activity. The test for CRP, however, remained positive and indicated the presence of an active inflammatory process.

OBSERVATIONS

The observations here reported confirm those of Anderson and McCarty who found the occurrence of C-reactive protein to be the most consistently positive laboratory test in the presence of rheumatic activity.[5]

It should be re-emphasized that the appearance of CRP in blood is a non-specific response to many inflammatory stimuli. The presence of certain manifestations and tissue lesions indicative of the rheumatic process in the absence of detectable amounts of CRP in the serum indicates that this process may continue below the threshold of the inflammatory stimulus required to produce a positive test. The detection of CRP in the serum therefore serves as an indicator of the intensity of an inflammatory process. Since a mild upper respiratory infection in itself is frequently sufficient to produce a positive test for CRP, the significance of a positive reaction in a rheumatic subject must be interpreted with caution. CRP will promptly disappear at the termination of an uncomplicated respiratory infection, in contrast to its usual persistence for several weeks, months or even years in association with active rheumatic fever.

At the present time there is no specific treatment available for rheumatic fever. The current aim of antirheumatic therapy with either adrenal cortical hormones or with salicylates is suppression of the inflammatory process in the hope that permanent valvular and myocardial scarring will be prevented or diminished. It is therefore helpful to know when suppression of the inflammatory process has been achieved. This may not be apparent by clinical criteria alone. While complete disappearance of CRP from the serum during therapy may not always indicate complete suppression of the rheumatic process, persistence of CRP during treatment certainly indicates that the inflammatory process is still active. It is therefore suggested that treatment be vigorous enough at least to effect reversal of a positive test for CRP to negative.

It has not yet been determined whether the disappearance of CRP from the blood during antirheumatic therapy is secondary solely to the suppression of the inflammatory reaction or whether the antirheumatic agents themselves directly suppress the production of this protein in the body. Although conclusive experimental data bearing upon this question is difficult to obtain, it has been demonstrated that pretreatment of patients with large doses of cortisone for several days will not prevent the appearance of CRP in the blood when a stimulus such as typhoid vaccine is administered intravenously, despite the simultaneous suppression of the expected rise in erythrocyte sedimentation rate.[12]

Despite these limitations, the test for CRP has been found to be a very useful addition to the armamentarium of the clinican for the management of the rheumatic patient. False positive tests do not occur since CRP is not present, even in trace amounts, in normal sera. Its performance is simple and it can be employed as a routine laboratory procedure if the specific rabbit antiserum is available. The major limitation to its general employment at the present time appears to be the difficulty of obtaining and purifying adequate quantities of human C-reactive protein which can then be used to immunize rabbits. This problem should not constitute a serious obstacle, however, since it has been demonstrated that C-reactive protein also appears in the blood and exudates of monkeys[13] and these animals may prove to be a convenient source of the required antigen. The possible application of the capillary precipitin test for CRP to the detection of active inflammation in other diseases such as tuberculosis, cancer and myocardial infarction should serve as an impetus to preparation of the specific antiserum on a larger scale.

Since the present study confirms the reliability and sensitivity of the detection of CRP in the blood as an indicator of the presence of rheumatic activity, the authors submit that this finding be added to the list of minor manifestations proposed by Jones[9] as criteria for the diagnosis of rheumatic fever.

SUMMARY AND CONCLUSIONS

Serial determinations of C-reactive protein in the sera of sixty-two patients were carried out during various stages of rheumatic fever and during treatment with various antirheumatic agents. The usefulness and limitations of this test for the detection of rheumatic activity is demonstrated.

The presence of C-reactive protein in the blood of a rheumatic patient is an extremely sensitive and reliable indicator of rheumatic activity if other unrelated pathologic processes can be excluded. Certain isolated rheumatic manifestations, however, may be present without causing the appearance of CRP in the patient's blood. These include chorea, erythema marginatum, subcutaneous nodules and Aschoff bodies in the auricular myocardium.

The disappearance of CRP from the blood is a good prognostic sign for the termination of a rheumatic attack but does not preclude the possibility of a future polycyclic recurrence.

Persistence of CRP in the blood during treatment with antirheumatic agents indicates inadequate suppression of the inflammatory process.

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Locally Administered Hydrocortisone in the Rheumatic Diseases*

A Summary of Its Use in 547 Patients

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ALTHOUGH most forms of arthritis and other rheumatic diseases are systemic rather than local in nature, they may be, in certain instances, manifested by inflammation in only one joint or few joints. In such circumstances local palliation has long been sought, either by physical therapy or by direct instillation of drugs into the affected joint.[3,16,24] Except for local anesthetics, however, locally instilled drugs have heretofore not been capable of consistently relieving local pain and swelling, and the relief afforded by the injection of local anesthetics has usually been too transient to be of practical value.

The physiologic effects of cortisone and hydrocortisone administered directly into diseased tissues have been studied extensively during the past two years. At a local, or tissue, level these hormones elicit responses similar to and often greater than those produced by parenteral or oral administration. Small doses applied at a site of inflammation produce a much greater local concentration than would be possible except by systemic administration of full anti-inflammatory doses of these hormones.

The possibility that intra-articular cortisone might be of practical value in palliation of local inflammation of the joint was investigated in this clinic. Clinical changes, intra-articular temperature[9] and other objective measurements of alterations of joint physiology were made following the intra-articular injection of 25 to 50 mg. of cortisone acetate into the diseased knees of seven patients with rheumatoid arthritis.[10] Although a definite anti-rheumatic effect was demonstrated in three of the patients studied, the relief of pain and stiffness was transient, and neither improvement in function nor decrease in swelling and tenderness could be demonstrated consistently. Repeated injections, even in the three patients who had originally responded favorably, did not reproduce consistently the desired effect; and we observed a marked though transient exacerbation of the local inflammation in several instances. From these preliminary observations it appeared that the degree and duration of the favorable response were insufficient and too inconsistent to be of clinical usefulness. Although others[8,14] reported somewhat better and more consistent results their conclusions appeared to be basically similar to ours.

While these observations were being made, data were accumulating which strongly suggested that hydrocortisone was the principal glycogenic steroid elaborated by the adrenal cortex.[2,12,15,17,18] In the laboratory the physiologic properties of cortisone and hydrocortisone appeared to be qualitatively quite similar; but, in general, hydrocortisone was quantitatively more effective. Depending upon what properties were being measured, this greater potency of hydrocortisone was estimated to be from twice to many times that of cortisone. Corrobo-

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ration of these data by sizable clinical studies was not possible before January, 1951, because of the scarcity of hydrocortisone.

In studies reported elsewhere[11] a comparative assay of cortisone acetate and hydrocortisone acetate was accomplished utilizing various objective methods of measuring improvement produced by the intra-articular administration of various doses of these preparations. A marked superiority of intensity and duration of activity, as well as consistency of local anti-rheumatic effect, was demonstrated for hydrocortisone.

Clinical trial of locally administered hydrocortisone in many types of arthritis and other rheumatic diseases produced encouraging results.[11] The small dosage utilized was not productive of systemic effects following such injections, and no significant local untoward effects were encountered. It was obvious at the outset that this type of "treatment," even though it might prove practicable, must be considered an adjunct to the general or systemic therapy for the rheumatic diseases, since few of these disorders are of local origin.

In order to define more clearly the possibilities of this method of adjuvant therapy, and to establish the indications for, contraindications to, and possible adverse effects of intra-articular hydrocortisone administration, an expanded study was undertaken.*

The purpose of this report is to summarize eighteen months of experience with 3,757 injections of hydrocortisone into the joints or other diseased connective tissue spaces of 547 patients suffering from various forms of rheumatic disease.

METHODS AND PROCEDURE

The presence of active arthritis or other local "rheumatic" inflammation, either acute or chronic, of any diarthrodial joints except those of the spine, or of any accessible bursa, tendon sheath or serous cavity, was the major consideration in selecting patients for the study. No attempt was made to exclude patients because of age, other associated disease or severity of destruction of the involved tissue. Because of the well known tendency of cortisone to reduce the local immune response to infection, no hydrocortisone injections were made into joints or other tissue spaces in which specific infection was known to exist.

* Grateful acknowledgment is made to Merck and Company for the supplies of hydrocortisone used in this study.

The technic of intra-articular injection of hydrocortisone suspension has been described in detail elsewhere.[11] Using the simple sterility precautions observed for any office or clinic injection procedure, the various joints were aspirated and the suspension introduced. The site of paracentesis for each joint was determined by that location where the synovial cavity was most superficial and relatively free of overlying large vessels or nerve trunks. Local anesthesia was seldom necessary once the operators had become familiar with the technic for each specific joint. By this simple and rapid method as many as thirty-five joint injections could be given by one physician in a three-hour clinic period.

The dosage of hydrocortisone employed was chosen empirically and ranged from 25 mg. for larger joints to as little as 5 mg. in finger or toe joints. The dose was increased for subsequent injections if the initial response was inadequate, but no more than 50 mg. were used in any joint at one instillation. Seldom were more than two joints injected at any one visit, in order that the total dose given would be insufficient to produce appreciable systemic effect.

Injections were repeated at intervals of from three days to several months, depending upon the rapidity of recurrence of symptoms and signs. On the average joints inflamed by rheumatoid arthritis required re-injection about once every ten days whereas in the case of osteoarthritic joints symptoms were apt to be allayed for longer periods (fourteen to twenty-one days) after an injection of hydrocortisone.

In nearly every instance this form of therapy was employed as a local adjunct to those established measures which have stood the test of time. All patients received physical therapy, orthopedic measures and systemic drug therapy as indicated.

Individual patient records were maintained throughout the study, recording in detail changes both in the local process and in the status of the general disease when these coexisted. The dose of hydrocortisone used, the technical success or failure of entering the synovial cavity as demonstrated by withdrawal of fluid, the occurrence of untoward reactions and improvement in terms of degree and duration of benefit in local symptoms and signs derived from the preceding injection were all recorded on the chart at each visit.

Observations were made to determine whether

the treated tissues might develop refractoriness or decreased local response comparable to that sometimes noted with systemically administered hormone therapy after long continuation. The records were also analyzed at intervals to determine the possible effects of local hydrocortisone injections on the course of the disease process, or on the responsiveness of these patients to general measures (e.g., gold therapy).

TABLE I

PATIENTS TREATED WITH LOCAL HYDROCORTISONE
ANALYSIS BY DIAGNOSIS AND RESULT

Diagnosis	No. of Patients	Case Successes*		Case Failures*	
		No.	Per cent	No.	Per cent
Rheumatoid arthritis	249	223	90	26	10
Osteoarthritis (except hip)	210	184	88	26	12
Osteoarthritis of hip	21	10	47	11	53
Gouty arthritis	18	18	100	0	0
Traumatic arthritis	16	15	94	1	6
Bursitis without arthritis	17	8	47	9	53
Disseminated lupus erythematosus	6	4	67	2	33
Periarteritis nodosa (joints)	3	3	100	0	0
Shoulder-hand syndrome	5	1	20	4	80
Parahemophilia (hemarthrosis)	1	1	100	0	0
Tuberculous arthritis	1	0	0	1	100
Totals	547	467	85.4%	80	14.6%

* See text for criteria.

RESULTS

A total of 3,757 injections of hydrocortisone suspension were made into the joints or other connective tissue spaces of 547 patients with arthritis or other rheumatic disease. The number of patients with each type of rheumatic disease is summarized in Table I.

Classification of results obtained by single or repeated injections of hydrocortisone in each patient was accomplished by categorical grouping as described hereinafter. A single injection resulting in unequivocal improvement in both symptoms (e.g., diminished pain, stiffness) and signs (e.g., decreased swelling, or at least improved function) in the treated joint for at least three days was regarded as an *injection success*. On the other hand an *injection failure* resulted when these minimal criteria were not fulfilled. Although marked benefit was obtained in many instances for twenty-four to forty-eight hours, and slight relief experienced for many days in some, they were classified as injection failures because these criteria were not entirely fulfilled.

When each of a series of injections into one or more arthritic joints of a single patient gave significant palliation for a period of time sufficient to be of practical value (i.e., one week or more) throughout the period of study, the results were classified as a *case success*. Patients not obtaining consistent benefit from repeated injections, or in whom continued re-injection was not considered worth while because of short duration or minimal benefit, were listed as *case failures*. For example, a patient who received a series of nine injections into a rheumatoid arthritic knee, half of which were injection failures, would be classed as a case failure since the beneficial effect of treatment was not consistent enough to prove of practical value for that patient. It should be noted that the patient or case results, as listed in Table I, are to be distinguished from the individual injection results summarized in Table II. Patients achieving successful over-all palliation of local inflammation frequently had one or a few injection failures and, contrariwise, those patients who achieved little over-all palliation during the study period often had one or a few injection successes.

From Table I it will be noted that the number of case failures in rheumatoid arthritis and

osteoarthritis (exclusive of hip joint disease) was quite low; but in osteoarthritis of the hip (malum coxae senilis) the poor results outnumbered the patients significantly benefited by repeated injection. This high incidence of failure was undoubtedly attributable, in many instances, to the technical difficulty of introducing a needle into the synovial cavity of the hip.

Whereas the incidence of case failures in bursitis was also high, it is noteworthy that each of the poor results in this category was in patients with *chronic* subdeltoid bursitis. Only one of five patients with the shoulder-hand syndrome responded satisfactorily to repeated instillation of hydrocortisone into the shoulder joint.

Through faulty diagnosis one patient with tuberculous arthritis of an ankle was inadvertently included in this series. Although the hydrocortisone injections initially suppressed the inflammation, exacerbation followed which necessitated surgical fusion and antibiotic therapy. This, therefore, was an instance of *injection success* but definitely a *case failure*.

Although the results obtained in the other disease states listed in Table 1 appear quite satisfactory, it must be emphasized that this was an evaluation of effects *at the site of injection only*. Even though hydrocortisone, locally administered into tissues inflamed by gout, periarteritis, lupus erythematosus or the hemarthroses of parahemophilia, consistently alleviated the symptoms and signs of the local involvement, there was no appreciable effect on the systemic disease process. Only where the disease may be localized and self-limited, as in traumatic arthritis, tendonitis or bursitis, was there complete and apparently permanent suppression of the disease process itself.

The follow-up of the 547 patients at the close of this study period is illustrated graphically in Figure 1. All patients were followed for at least one month after single or repeated injections, and fifty-nine patients in these several categories were re-injected and followed for periods over one year.

In the upper portion of the chart are noted the 106 patients (20 per cent) who had no return of symptoms after one or a series of injections. In this group are included many of the self-limited conditions, such as traumatic arthritis, acute bursitis and acute attacks of gout (cf. Table 1) that have not, at the time of this writing, recurred. It is worthy of note, however, that forty-two of 210 cases of osteoarthritis fell into this group; indeed twelve of these have required no further injections even though it has been more than one year since the last. Thirty-one cases of rheumatoid arthritis have had persistent remission in the injected joints; but in many of these, gold therapy, phenylbutazone, systemic cortisone or a spontaneous remission in the disease may well have been responsible, since uninjected joints have also improved. Intra-articular hydrocortisone injections, even though in some cases repeated more than thirty times in a single joint, did not appear to impede the occurrence of spontaneous or therapeutically induced remissions in the systemic disease process.

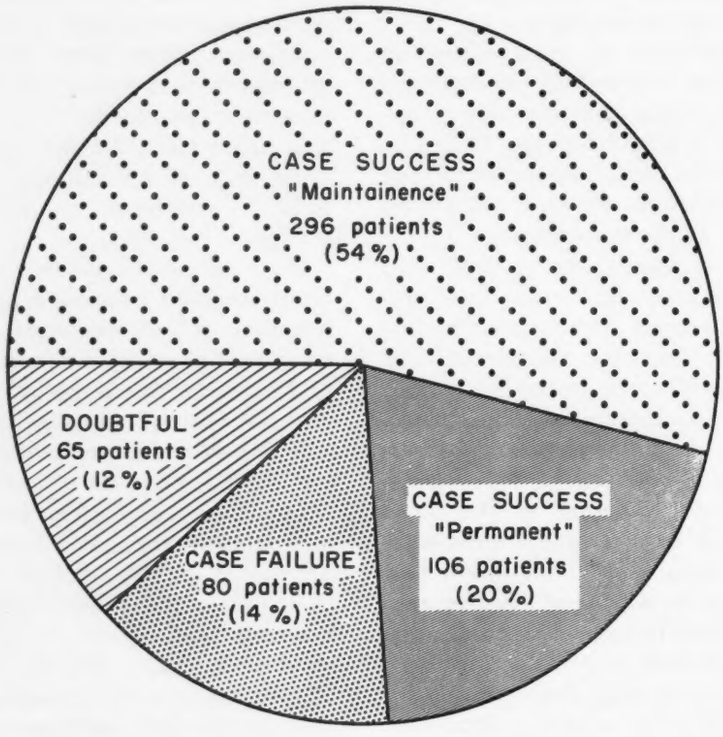
A group of 296 patients (54 per cent of the total) received continued local palliation from injections of hydrocortisone repeated as often as symptoms returned (i.e., every one to four weeks or more). In this large group are most of the patients with rheumatoid arthritis and osteoarthritis. Many patients observed that succeeding injections had an increasingly greater beneficial effect (i.e., greater relief for longer periods) but, contrariwise, an occasional patient noted decreasing effects, though still beneficial. In these latter cases increasing the dose of the hormone (e.g., 25 mg. to 37.5 mg.) frequently resulted in greater benefit. In general, however, careful observations throughout the study in no instance revealed significant evidence to suggest the development of a state of "tolerance," or an induced local diminution of tissue responsiveness to the instilled hydrocortisone. This appeared to be true regardless of the frequency of injection (as often as every three days) or the duration of the study period (as long as eighteen months).

Sixty-five patients were classified as *doubtful* because follow-up evaluation was inadequate or unavailable. This group is constituted primarily of patients receiving one or more intra-articular injections classified as an *injection success*. In no instance was a patient included in this group if a known untoward reaction occurred following an injection. If more than one or two *injection failures* appeared in their record, they were placed in the total failure group.

Obviously no final conclusions can be drawn from the data resulting from the incomplete studies in this group. Included also in this group are seven patients who died from causes apparently not attributable to the intra-articular therapy. Peculiarly, all seven patients were re-

ceiving systemic cortisone therapy for severe disease and the hydrocortisone was being used as a local adjunct in "resistant" joints. One patient died of a subdural hemorrhage following a fall down the steps in her home, one as a result of a subarachnoid hemorrhage sustained in a brawl, one from uremia associated with disseminated lupus erythematosus, one from multiple bowel hemorrhages from periarteritis nodosa, one from peritonitis following the perforation of a sigmoid diverticulum (six days after operation), one from a cerebrovascular accident, and one from a coronary occlusion. Since none of these deaths occurred within a week following the last intra-articular injection, and were clearly explained by other conditions, they have not been attributed to local hydrocortisone injection. Further, they have not been classified as "case failures" since the intra-articular injections were consistently of considerable benefit locally.

As previously described the eighty patients classified as *case failures* in Figure 1 are distributed among the various diagnostic categories in Table I.



LEGEND

CASE SUCCESS (Permanent)	*One or more local injections successful so that no further treatment was required.*
CASE SUCCESS (Maintainence)	*Repeated interval injections productive of continued benefits.*
CASE FAILURE	*Insufficient benefit or total failure after repeated trials.*
DOUBTFUL	*Follow-up inadequate.*

FIG. 1. Summary of case follow-up on 547 patients following repeated local injections of hydrocortisone.

ANALYSIS OF RESULTS BY SITE OF INJECTION

As summarized in Table II the joints most frequently injected were knees. This was partly because knees are so frequently involved and so often disabling in the various forms of arthritis; and because the knee joint is so large and superficial, making it easily accessible for intrasynovial injection. Rheumatoid arthritic knees

were injected 1,758 times; osteoarthritic knees, 1,034 times; and inflamed knees from other causes, fifty-five times. Probably because of the ease of paracentesis of this joint the incidence of failure to obtain beneficial results is singularly low. The incidence of failures by joints as seen in Table II is almost directly proportional to the technical difficulty of paracentesis of the joints in question. Unless the hydrocortisone suspension is introduced directly into the synovial cavity, little or no benefit follows. By reviewing the records made at the time of the individual injections, it was found that the large majority of *injection failures* occurred after injections when some doubt was recorded that the joint space had actually been entered (i.e., no synovial fluid was obtainable by aspiration, etc.). In 17 per cent of the instances of failure to receive benefit from injection, however, the injection had been made directly into the synovial sac, as proved by withdrawal of synovial fluid into the syringe before and after introducing the hydrocortisone. Why these injections were unsuccessful is not known. In some of these cases previous and subsequent injections were successful.

TABLE II

ANALYSIS OF RESULTS OF INJECTIONS OF HYDROCORTISONE "INJECTION FAILURES"

Site of Injection	Rheumatoid Arthritis			Osteoarthritis			Miscellaneous (Gout, Traumatic, etc.)			Totals		
	Total Injections	Failures		Total Injections	Failures		Total Injections	Failures		Number Injections	Failures	
		No.	Per cent		No.	Per cent		No.	Per cent		No.	Per cent
Knee	1,758	43	2.4	1,034	100	10	55	2	4	2,847	145	5
Ankle or tarsal	149	21	14.1	7	2	28	13	0	0	169	23	14
Wrist	119	38	32	6	1	17	16	0	0	141	39	28
Phalangeal	74	3	4	54	9	17	8	0	0	136	12	9
Elbow	91	2	2	18	1	6	25	3	12	134	6	4
Hip	52	12	23	77	37	48	0	0	.....	129	49	38
Shoulder	30	3	10	4	3	75	11	9	82	45	15	33
Temperomandibular	5	4	80	3	1	33	0	0	.....	8	5	62
Sternoclavicular or acromioclavicular	5	1	20	2	1	50	0	0	.....	7	2	28
Subdeltoid bursa												
Acute	0	0	....	0	0	....	24	4	17	.....	...	.....
Chronic	0	0	....	0	0	....	49	29	60	73	33	45
Other bursae												
Olecranon	36	5	14	.....	...	....	3	0	0	.....	...	.....
Prepatellar	0	0	....	1	...	....	...	..	.....	.....	...	.....
Bunion	6	2	33	.....	...	....	...	..	.....	46	7	15
Tendon sheaths	0	0	....	7	2	28	5	2	40	12	4	33
Pleural cavity	0	0	....	0	0	....	8	4	50	8	4	50
Pericardial cavity	0	0	....	0	0	....	2	2	100	2	2	100
Totals	2,325	134	6%	1,213	157	13%	221	55	24%	3,757	346	9%

In the injections of hydrocortisone into bursae for local inflammation, several points are worthy of presentation. Whereas the treatment of *acute* bursitis of the shoulder by intrabursal hydrocortisone was successful in achieving prompt and lasting relief in twenty of twenty-four instances, 60 per cent of injections for *chronic* subdeltoid bursitis were failures. Olecranon bursitis, so common in rheumatoid arthritis, responded quite well to the instillation of hydrocortisone, often with disappearance of swelling for many months. One injection into an olecranon bursa for gouty bursitis and two for traumatic bursitis

were likewise successful. The one case of prepatellar bursitis, previously reported, remains asymptomatic at this writing. Even bunions responded to injection of hydrocortisone into the adventitious bursal sac.

Injections of hydrocortisone into tendon sheaths of the hand for "trigger finger" or for deQuervain's stenosing tenosynovitis were beneficial in two-thirds of the instances, and complete relief has persisted as long as thirteen months in four cases. Here, as in chronic subdeltoid bursitis, it was difficult to be sure the hormone suspension was injected into the sac or sheath, so that many of the failures might have been due to failure of proper placement of the needle.

Sufficient experience with the instillation of hydrocortisone into the inflamed pleural and pericardial cavities of disseminated lupus erythematosus has not accumulated to support any conclusions as to practical effectiveness. No further intrapleural injections have been necessary in one of the two previously reported patients. In the other, however, the first few injections appeared to be helpful in retarding the return of pleural effusion; but subsequent aspiration and injection of hydrocortisone had little effect on the exudation.

In one patient with pericardial effusion from lupus erythematosus, two successive aspirations of the pericardial sac with instillation of 100 mg. of hydrocortisone suspension failed to yield appreciable benefit. Further experience will be necessary to assess properly the usefulness of locally instilled hydrocortisone in these circumstances.

CONCOMITANT SYSTEMIC THERAPY

Efforts to determine from our data whether concurrent "specific" therapy influenced the patient response to local hydrocortisone, or vice versa, was not productive of clear-cut evidence one way or the other. Twenty-nine of the rheumatoid arthritics received gold salts throughout this study; seventy-one were on a systemic cortisone regimen; and five were receiving ACTH. Seven patients were receiving combined gold salts and cortisone. Thirty-seven were receiving concomitant phenylbutazone orally. Although apparent alterations appeared in many patients' diseases, both spontaneously and presumably as a result of their systemic therapy, there were no systemic changes observed which could be attributed directly to the use of hydrocortisone locally. General systemic improvement frequently minimized or even obviated further need for local therapy and, of course, the opposite was observed.

In this eighteen-month period the largest number of injections given in succession in any one joint was thirty-three, and the largest number of joint injections received by any single patient was forty-seven. Twenty-seven patients received more than twenty injections into a single joint.

TABLE III
ADVERSE REACTIONS FROM HYDROCORTISONE INJECTIONS

Type	No.	Total Injection Per cent
Local exacerbation (2–72 hr.)	61	1.6
Local weakness (4–96 hr.)	11	0.3
Generalized weakness, vertigo, malaise (12–96 hr.)	10	0.3
Urticaria after injection	4	0.1
Infection of joint from injection	1	0.03
Possible aggravation of tuberculous arthritis	1	0.03
Total adverse reactions	88	2.3%

ADVERSE REACTIONS TO LOCAL HYDROCORTISONE

A total of eighty-eight untoward responses followed local administration of hydrocortisone. This constitutes but 2.3 per cent of the total 3,757 separate injections. As will be seen in Table III the great majority of these were temporary local exacerbations of the joint inflammation. They appeared within a few hours following injection in most patients but were delayed nearly twenty-four hours in a few. The duration of this superimposed acute arthritis varied from two to seventy-two hours. Although in some instances this was alarming and extremely painful, it was temporarily incapacitating in only a few. It should be noted that this reaction, even in its more severe form, did not discourage these patients from returning promptly for further injections. In no instance did we see such exacerbations last longer than seventy-two hours and, more often than not, actual improvement over the pre-injection state was noted, occurring some twenty-four to forty-eight hours after the reaction had disappeared. Microbiologic and other studies designed to determine the cause of these reactions have not been revealing. The use of codeine, ice packs,

immobilization of the involved joint and aspiration of tense effusions, when present, effectively controlled the more severe reactions. We have not considered the occurrence of such reactions to be contraindications to further local therapy at the same or other sites, and to date only two of our patients have experienced more than one of these episodes despite repeated subsequent injections.

A bizarre transient weakness was described by eleven patients, occurring in the extremity of the injected joint. This was never disabling and usually disappeared within a few hours. Even the most protracted of these reactions did not exceed three or four days, and in no instance were we able to find evidence to support an organic origin for this complaint. A similar number of patients experienced a generalized weakness, associated with malaise and "lightheadedness." This followed a similar innocuous and transient course, and was again of obscure origin. These two types of undesirable responses are unexplained and warrant further observation, but have not, to date, been of clinical importance because of their rarity and benign characteristics.

Hypersensitivity was observed in only four patients and was manifested by urticaria in all instances. Concomitant procaine HCl 1 per cent, used to obtain anesthesia at the site of local therapy, was responsible for allergic reaction in three of these patients; and the fourth was found to be hypersensitive to suspending agents in the aqueous vehicle of the hydrocortisone suspension. Intradermal testing of the diluted substances involved was employed in determining the cause of each reaction.

Although nearly 4,000 injections were made into locally diseased tissues, in only one was infection introduced into the site under study. An acute staphylococcic arthritis was superimposed in the rheumatoid diseased knee of this patient. The patient was on a systemic cortisone regimen and had a mild acneiform dermatitis involving the skin through which the needle was introduced. The infection was quickly controlled with an antibiotic. Obviously, better judgment in selection of injection site would probably have avoided this one experience. It is noteworthy that this was the only joint infection to occur even though only the routine sterility precautions of office or clinic practice were used. Drapes and gloves were never employed.

COMMENTS

It should be emphasized that the established general therapy for all of these rheumatic states was begun before or concurrently with initiation of local hydrocortisone injections. In essentially every instance such local therapy was employed as an adjuvant to general therapeutic measures. The results were of necessity interpreted with the knowledge that other treatment was, in many instances, contributing to observed alterations in the course of the disease. The natural cycles of remission and relapse and the distinct changes in the rheumatic diseases often produced by any treatment, especially one in which a new medicine is instilled directly into the site of discomfort, presupposes major improvement in a few patients and minor improvement in many. It was believed that the large number of patients and the variety of disorders would serve to define those instances in which significant therapeutic usefulness was obtained. At the same time the indications and contraindications could be more clearly delineated. Further, it appeared likely that a more accurate assessment of predictable untoward responses would result. Finally, only through the consistent corroboration of others[1,4–8,13,14,19–23,25] and by clinical trials over long periods of time can any agent be accepted as established treatment of the rheumatic diseases.

Although the total duration of these observations is short in relation to the course of many of these chronic rheumatic diseases, we believe that this study has accomplished many of the foregoing objectives. We conclude that the following may be areas of usefulness or need for local therapy with hydrocortisone: (1) Suppression of acute or chronic inflammation of one, or at most a few, peripheral joints. Inflammation caused by infection is, of course, excluded. (2) Suppression of acute or chronic non-specific inflammation of bursae and tendon sheaths. (3) Therapeutic control of one or a few painfully disabling joints even in the presence of widespread joint disease. (4) Suppression of local disease in a few of the more actively involved joints while systemic therapy effects its more slowly evolved benefit, or where systemic therapy is contraindicated. (5) Therapeutic control of more resistant joints, allowing maintenance on systemic therapy either more effectively or at a lower total dosage level. (6) Suppression of inflammation in joints showing early but actively progressive deformity, enhanc-

ing the effect of physiotherapy, orthopedic and general corrective measures. (7) Suppression of joint inflammation in preparation for or following surgical or other orthopedic measures.

Contraindications to the use of hydrocortisone locally are: (1) The presence of proven or suspected infection in or near the joint. Local instillation of hydrocortisone into or through such diseased tissues may spread the infection. (2) Proven or suspected hypersensitivity to either hydrocortisone or the constituents of the suspending vehicle. This may, in some cases, contraindicate its use.

Our experience has prompted us to infer that little if any benefit is to be expected and certain dangers may be inherent in the local administration of hydrocortisone in some circumstances. These may be listed as follows: (1) Diseased spinal joints do not lend themselves to this type of therapy either because of anatomic inaccessibility or multiplicity of joints involved. (2) The joints devoid of synovial space cannot usually be successfully treated in this manner (e.g., the sacroiliac joints, etc.). (3) Generalized active involvement of multiple joints usually makes this type of therapy futile unless one or a few joints become outstanding problems (e.g., weight-bearing joints). (4) After several trials with resultant therapeutic failure, repetition of local treatment is usually useless. (5) After severe trauma with derangement and/or fracture of the bones or other joint tissues, repeated instillation of hydrocortisone may be contraindicated because of the theoretic hazard of inhibiting normal healing. (6) Local therapy without a clear understanding of the possible precipitating or aggravating factors of the underlying disease process is to be avoided. Comprehensive therapy, including orthopedic correction and physiotherapeutic measures, must be utilized wherever indicated.

SUMMARY

1. Hydrocortisone has been injected into inflamed joints or other non-infectious locally diseased tissues a total of 3,757 times in 547 patients with various types of rheumatic disease over an eighteen-month period. This includes 249 patients with rheumatoid arthritis and 210 with osteoarthritis.

2. Repeated intra-articular or intrabursal hydrocortisone injections at least partially alleviated the local inflammation in 85 per cent of patients treated. An analysis of case results is given.

3. Individual injections of the hormone failed to produce appreciable therapeutic benefit in 346 of 3,757 instances (9 per cent). An analysis of the results with individual joints is presented.

4. Indications for and contraindications to this method are presented.

5. Adverse reactions to this local therapy are few and transient.

6. Intra-articular hydrocortisone is a useful adjunct to the usual methods of treatment for rheumatoid arthritis, osteoarthritis, gout, bursitis and other localized rheumatic disorders.

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The Sprue Syndrome Secondary to Lymphoma of the Small Bowel*

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ALTHOUGH the vast majority of cases of the sprue syndrome are of the so-called idiopathic varieties—tropical and non-tropical—there are several groups of diseases which give rise to symptomatic or "secondary" sprue. These include: (1) inflammatory diseases of the small bowel such as active regional enteritis and ulcerative tuberculous enterocolitis;[4,6] (2) occlusion of the lymphatic drainage of the small intestines—tabes mesenterica,[19,22,24] lipophagic intestinal granulomatosis (Whipple's disease),[5,18,29] lymphangiomatous cysts of the mesentery,[4] and small intestinal lymphoblastomas.[1,3,4,13,16,17,25,26] Altered anatomy of the gastrointestinal tract may also give rise to symptomatic sprue, as in gastrojejunocolic fistula,[12] as a complication of partial or total gastrectomy[11,20,23,30] or following massive resection of the small bowel.[2]

In 1947 one of us (D. P. B.) reported a case of intestinal lymphoblastoma in which extensive metabolic studies demonstrated the typical absorptive defects of the sprue syndrome.[17] Since that time we have observed three cases of sprue secondary to intestinal lymphoblastomas at the New York Hospital; yet a review of the literature yields only thirteen other cases of sprue secondary to lymphoblastoma of the small bowel and mesentery. This contrast may indicate that, although the association is rare, it may at times go unrecognized. For this reason we present here a summary of these cases, together with a comparison with a similar number of cases of idiopathic non-tropical sprue, diagnosed and treated during the past twenty years at the New York Hospital. We have omitted from consideration all cases of tropical sprue.

CASE REPORTS

CASE 1. B. K. (No. 14, Table 1), a forty-nine year old white housewife, was admitted to the New York Hospital on July 21, 1941, because of diarrhea for nine months.† Approximately nine months before admission she had the insidious onset of a diarrhea of four to six copious, light, foul stools daily, followed by increasing weakness. She was found to have anemia and was treated with liver, iron and transfusions There was a rise in hemoglobin but no change in her diarrhea. She lost 50 pounds in weight.

On physical examination, the patient was an emaciated, sallow, chronically ill woman with muscular wasting. Blood pressure was 90/70. There was moderate distention of the abdomen, and a firm mass was felt in the right lower quadrant, 5 cm. in diameter, which was found to move with the uterus. Chvostek and Trousseau signs were positive. Deep tendon reflexes were absent except for the knee jerks. There was no lymphadenopathy or hepatosplenomegaly.

Laboratory data were as follows: red blood cells, 6.6 m./mm.^{3}; hemoglobin, 12.5 gm./100 cc.; white blood cells, 9,300 and Kline negative. Analysis of the serum showed: total protein, 5.0 gm./100 cc.; calcium, 4.8 mg./100 cc.; phosphorus, 2.2 mg./100 cc.; potassium, 1.3 mEq./L.; sodium, 139.8 mEq./L. Plasma prothrombin was 63 per cent. The stool contained 30.1 per cent fat dry weight.

Gastric analysis showed 8 units of free hydrochloric acid thirty minutes after histamine. An oral glucose tolerance curve on two occasions was flat. Pancreatic enzymes following secretin were normal. X-ray study of the gastrointestinal tract showed loss of the normal mucosal pattern of the jejunum and delayed transit of barium.

The patient was treated with a high simple carbohydrate, high protein, low fat diet with supplemental vitamins, calcium, potassium and liver extract. On this regimen she improved

† This case was previously reported in detail.

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slightly but weakness and diarrhea persisted. After several weeks intensive vitamin D therapy was begun, starting at 500,000 units and gradually increasing to 4,000,000 units daily. During this period she showed striking improvement with diminution of diarrhea, increased muscular strength, and return of serum calcium, phosphorus and potassium to normal or near normal levels. On this regimen she remained fairly well. In March, 1943, the patient developed increasing intestinal obstruction over a period of several weeks. At operation an obstructing mass was found in the ileum. She rapidly declined and died in May, 1943. Autopsy revealed extensive tumor involving chiefly the small bowel, mesenteric and para-aortic lymph nodes with widespread metastases. Microscopically all the tumor examined consisted of anaplastic lymphosarcoma.

CASE II. W. D. (No. 15, Table 1), a forty-six year old white taxi cab driver was admitted to the New York Hospital for the first time on January 25, 1946, because of diarrhea and abdominal cramps. The patient had been well until seven months prior to admission when he had an attack of diarrhea consisting of from four to seven loose stools daily which lasted three to four days. One month prior to admission the diarrhea reappeared; the movements were preceded by abdominal cramps and borborygmi. The stools were copious, light brown and foul. He became anorexic, weakened and lost 50 pounds in weight. For one month preceding entry he had had moderate ankle edema and for two weeks numbness and tingling of his hands and feet.

On examination the patient was extremely emaciated and chronically ill, with sunken eyes and marked muscular wasting. Blood pressure was 100/74. There was a reddened, partially smooth tongue, enlarged tympanitic abdomen, clubbing of the fingers and toes, moderate pitting edema of both ankles, absent deep tendon reflexes except for the right triceps and knee jerks, and a positive Trousseau sign. Liver, spleen and lymph nodes were not enlarged.

Laboratory data were as follows: red blood cells 3.9 m./mm.^{3}, white blood cells 10,000, and Mazzini negative. Analysis of the serum showed: total protein, 4.9 gm./100 cc. with an A/G of 2.8/2.1; calcium, 5.5 mg./100 cc.; phosphorus, 2.3 mg./100 cc.; sodium, 136 mEq./L., and chlorides, 102 mEq./L. The stool contained 36 per cent fat dry weight.

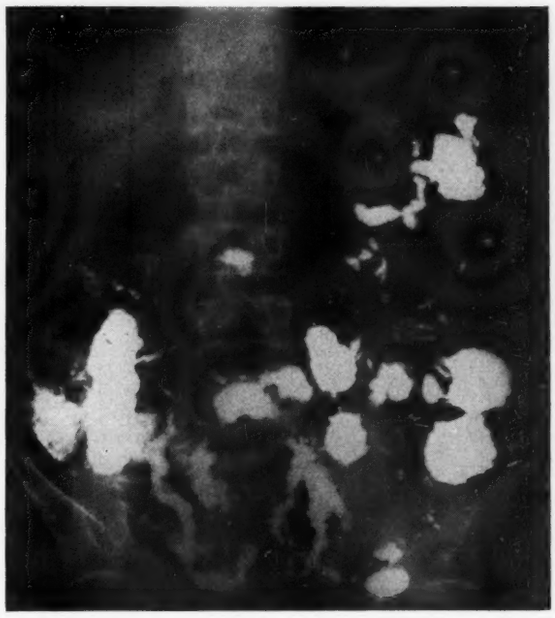
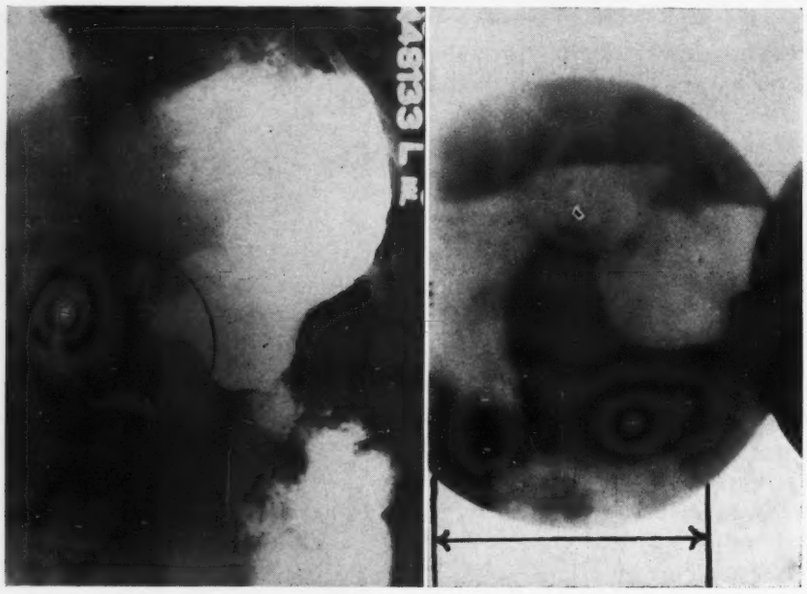


FIG. 1A. Case II. Small bowel series showing typical "deficiency pattern" of non-tropical sprue. In none of our cases were the roentgenologic findings considered characteristic of lymphosarcoma.

An oral glucose tolerance test on repeated occasions was flat; sternal marrow smear was interpreted as consistent with "nutritional" anemia. X-ray of the small bowel revealed a deficiency pattern characterized by dilatation of some loops with segmentation and flocculation and delayed transit. (Fig. 1A.)

A diagnosis of non-tropical sprue was made and the patient was treated for three months with a high calorie, high protein, low fat diet with added vitamins, calcium and folic acid. His clinical condition improved; the appetite returned, diarrhea, edema and distention disappeared and he gained 18 pounds. Albumin rose to 4.7 gm./100 cc. and calcium to 10 mg./100 cc.

This regimen continued, with further gain in weight of 37 pounds. He returned to work as a cab driver, felt well and had one to two formed stools daily. After eleven months he suddenly developed symptoms of upper small bowel obstruction. A gastrointestinal series revealed an irregular constriction in the second portion of the duodenum; the small bowel was otherwise not remarkable. (Fig. 1B and C.) At operation a malignant lesion of the second, third and fourth portions of the duodenum was found and was widely resected. Pathologic findings showed it to be a primitive retothelial sarcoma of the duodenum with invasion of the pancreas. After



1B 1C

FIG. 1. B, filling defect of the second portion of the duodenum due to reticulum cell sarcoma; C, spot film of area circled showing extent of obstruction.

operation the patient developed peritonitis and shock, and expired. No autopsy was obtained.

CASE III. B. V. (No. 16, Table 1), a thirty-three year old white female mechanic, was admitted to the New York Hospital on September 8, 1947, because of swelling of the lower extremities and lower trunk of four years' duration. In 1938 the patient had generalized lymphadenopathy including large masses in the submandibular and epigastric areas. A diagnosis of Hodgkin's disease was made after lymph node biopsy. X-radiation resulted in disappearance of the masses. In 1945 an abdominal mass appeared which also responded to radiation. In 1947 the patient had a hysterosalpingo-oophorectomy at which time no abnormal masses were noted in the abdomen.

On examination the patient did not appear ill. Blood pressure was 110/70. There was marked pitting edema of the lower portion of the body extending up to TII posteriorly and to the costal margins anteriorly, greatest in the most dependent portions of the body and decreasing centrally. There was no periorbital edema. Breath sounds were decreased at the lung bases. Liver, spleen and lymph nodes were not enlarged.

Laboratory data were as follows: red blood cells, 5.9 m./mm.^{3}; hemoglobin, 14.9 gm./100 cc.; white blood cells, 6,000. Analysis of the serum showed: total protein, 2.9 gm./100 cc. with an A/G of 2.1/0.8; calcium, between 8.5–10.5 mg./100 cc.; chlorides, 104 mEq./L. The stool contained 24 per cent fat dry weight while the patient was on a low fat diet.

An oral glucose tolerance test was normal as was the pancreatic enzyme response following secretin stimulation.

Shortly after admission the patient began to have frequent, bulky, light, foul stools which continued intermittently throughout the hospital course. She was given a high protein, high calorie diet with gradual decrease in the fat content. The regimen also included infusions of plasma, albumin and amino acids. There was some decrease in the number of stools, and the loss of some edema fluid, but no rise in her serum albumin. On March 12, 1948, the patient suddenly lost consciousness and thrashed wildly in her bed. Symptoms and physical findings were consistent with acute damage to the right cerebral hemisphere. She developed symptoms of increasing intracranial pressure. An emergency craniotomy was carried out, with aspiration of the right cerebral hemisphere and decompression, but the patient never regained consciousness and soon expired. Postmortem examination revealed extensive neoplastic infiltration of the small bowel, particularly the terminal ileum, and of the mesenteric and paraaortic lymph nodes. Microscopically, the tumor was a giant follicle cell lymphoma.

CASE IV. C. D. (No. 17, Table I), a sixty-eight year old retired male bookkeeper, entered the New York Hospital for the first time on January 12, 1951, because of diarrhea. About four weeks prior to admission the patient began to have five to six liquid, yellowish, foul, foamy stools daily, together with anorexia and a 10 pound weight loss.

On examination the patient was a thin, emaciated, elderly male with evidence of recent weight loss. The blood pressure was 80/60. There was bilateral nerve deafness, emphysema, and a distended, tympanitic abdomen. The tongue was normal and there was no enlargement of liver, spleen or lymph nodes.

Laboratory data were as follows: red blood cells, 4.1 m./mm.^{3}; hemoglobin, 12.1 gm./100 cc.; white blood cells, 5,900. The Mazzini test was negative. Analysis of the serum showed: total protein, 4.3 gm./100 cc. with an A/G of 3.2/1.1; calcium, 4.1 mg./100 cc.; phosphorus, 2.8 mg./100 cc.; potassium, 2.5 mEq./L.; sodium, 131 mEq./L.; chlorides, 101 mEq./L.; prothrombin time was normal. Stools were grossly fatty.

An oral glucose tolerance curve was flat; gastric analysis revealed no free acid in the fasting specimen and 57 units thirty minutes after histamine. X-rays of the gastrointestinal tract showed an abnormal motor pattern in the small intestine with delay in transit. Pancreatic enzymes following secretin were normal.

The working diagnosis was non-tropical sprue. The therapy consisted of a high calorie, high protein, high simple carbohydrate, low fat diet with large supplements of vitamins and calcium, and parenteral liver extract. On this program he improved remarkably, with cessation of diarrhea, return of strength and appetite, recession of abdominal distention and maintenance of increased weight. This remission lasted ten months.

In November, 1951, diarrhea recurred and the patient had a massive gastrointestinal hemorrhage with passage of tarry stools and dark blood. On admission to the hospital intensive study revealed only questionable x-ray evidence of polyps in the transverse colon. Laboratory data were the same as on the previous admission except for a markedly elevated prothrombin time of 57.2 seconds with a control of 16.0 seconds. It was thought that the low prothrombin activity might have led to hemorrhage from the polyps. The patient responded to parenteral vitamin K and blood transfusions, and the bleeding ceased.

Six weeks later, on January 23, 1952, the patient came to the emergency ward because of sudden, severe abdominal pain followed by chills and fever. Physical examination revealed a temperature of 40°c., pulse 112, blood pressure 90/50 and respirations 30. He was acutely and chronically ill, pale, and complaining of severe, generalized abdominal pain. The abdomen was markedly distended and rigid with generalized rebound tenderness and absent bowel sounds. A flat film of the abdomen showed air beneath the right diaphragm.

At laparotomy a perforation of the upper jejunum approximately 20 cm. from the ligament of Treitz was found in an area of thickened bowel whose mesentery was likewise thickened and studded with enlarged, firm lymph nodes. A resection of this diseased jejunum with its mesentery was performed. The pathologic report on the specimens was Hodgkin's sarcoma of the jejunum and mesentery.

Following operation the patient received radiation therapy to a total of 2,600 r through several portals to the abdomen. Although up and about, his clinical condition remained poor. He died in a nursing home twelve weeks after operation. Autopsy revealed no evidence of Hodgkin's sarcoma in the abdomen or in any organ.

COMMENT

The clinical features of three of these cases corresponded to the classic picture of non-tropical sprue. The history, physical findings and laboratory data all pointed to serious deficiency of intestinal absorption. Case III had diarrhea, steatorrhea, nutritional edema and hypoproteinemia, and a "deficiency pattern" of the small bowel on x-ray examination; she showed improvement of diarrhea and steatorrhea on a low fat diet; on the other hand, the oral glucose tolerance test and blood calcium were normal.

Between September, 1932, and January, 1952, twenty-five cases of non-tropical sprue have been treated at the New York Hospital. Twenty of these have been of the idiopathic variety, one due to tabes mesenterica, and the remaining four are the above reported cases. These latter cases are strikingly similar to thirteen cases of sprue secondary to a lymphoblastoma of the small bowel and mesentery culled from the

TABLE I

SUMMARY OF FINDINGS IN LYMPHOMA GROUP

Authors	Case No.	Age	Sex	Duration, Onset Sx to Medical Study (mo.)	Temporary Response to Sprue Regimen	Pathology and Location of Lesion	Duration of Life from Onset Sx (mo.)	% Fat of Dried Stool	Oral Glucose Tolerance	Calcium mg./ 100 cc. Serum	Small Bowel X-ray	RBC $\times 10^6$/ mm.^{3}	HGB gm./ 100 cc. or %	Color Index	Tongue Sx and Signs
Fairley, Mackie[13]	1	62	M	1	0	Lymphoma of mesentery glands; inflammation, jejunum and ileum	9	55	not done	5.0	not done	3.6	74	1.0	+
	2	42	F	? Few yr.	0	Large glands of mesentery; biopsy inguinal gland; Hodgkin's disease; intestinal obstruction	no follow-up	75.3	flat	10.0	not done	4.24	80	<1.0	+
	3	32	F	7	+	Abdominal mass; biopsy skin nodule; lymphosarcoma	11	30	flat	not done	not done	4.4	84	<1.0	0
	4	60	M	?	+	Inguinal node biopsy; Hodgkin's disease	no follow-up	51.5	not done	not done	not done	0.99	25	>1.0	+
Salvesen, Kobro[26]	5	60	M	8	0	Lymphogranulomatosis; jejunum and mesentery; perforation	10	45.0	low	8.4 mg.	normal	4.23	79	<1.0	+
	6	57	M	9	0	Inflammatory ulcers, jejunum; probable lymphogranulomatosis, mesentery	10	47	normal	not done	not done	normal	normal		
Bickel, Rutishauser[3]	7	60	M	"few"	+	Hodgkin's disease, ileum, mesentery, jejunum; ulcers	12	80 of ingested fat	normal	6.5	deficiency pattern	3.25	82	>1.0	+
Fritzche[16]	8	45	M	2½	0	Lymphosarcoma jejunum, ileum and mesentery; hemorrhage	5	fatty stools	not done	not done	Schwere jejunitis	4.3	86	1.0	0

(Had received Rx before seen by authors)

Adlersberg, Schein[1]	9	40	M	6	0	Lymphosarcoma of small intestine and mesentery; intestinal obstruction	14	47	flat	not done	deficiency pattern	4.4	93	1.0	0
Salvesen[25]	10	53	M	18	0	Lymphosarcoma jejunum and mesentery; perforation	20	16.3	low	7.3	normal	2.76	79	>1.0	0
Bjerkelund[4]	11	55	M	3	0	Lymphosarcoma of small bowel and mesentery	3	300–950 gm. fat in stools daily	normal	9.2	constriction and dilatation of loops	4.81	98	1.0	not mentioned
	12	55	M	3	0	Lymphogranulomatosis small bowel and mesentery	6	62	not done	5.5	not done	3.66	82	>1.0	+
	13	44	M	12	+	Lymphogranulomatosis small bowel and mesentery	24	39	low	7.6	deficiency pattern	3.95	96	>1.0	+
Sleisenger, Almy, Barr (1952)	14 (B. K.)	44	F	9	+	Lymphosarcoma, small and large bowel, mesentery; intestinal obstruction	29	30	low to flat	4.8	deficiency pattern	6.6	12.5	<1.0	0
	15 (W. D.)	46	M	7	+	Lymphosarcoma duodenum and mesentery; intestinal obstruction	21	36	flat	5.4	deficiency pattern	3.9	13.5	>1.0	+
	16 (B. V.)	33	F	48 (diarrhea 5 mo.)	+	Giant follicle cell lymphoma small bowel, terminal ileum and mesentery	5	24*	normal	8.5	deficiency pattern	5.9	14.	<1.0	0
	17 (C. D.)	68	M	1½	+	Hodgkin's sarcoma of jejunum and mesentery; perforation of jejunum, hemorrhage	17	not done	flat	4.1	deficiency pattern	4.1	12.5	1.0	0

* Patient on a low fat diet.

literature; this brings the total number of reported cases to seventeen.

Comparison of data on the seventeen cases of sprue secondary to lymphoblastoma—the "lymphoma" group (group I), with twenty New York Hospital cases of primary non-tropical sprue—the "idiopathic" group (group II), reveals some important similarities and differences. (Tables I and II.)

There was slight difference in the average age of the two groups, 50.3 and 45.5 years of age in the "lymphoma" and "idiopathic" groups, respectively. Thirteen males and four females comprised the former group and sixteen females and four males were in the latter. The sex ratio in the "lymphoma" cases is about the same as for all lymphosarcoma of the small intestine. This 4:1 sex ratio is reversed in the "idiopathic" group.

Excluding our Case III (No. 16, Table I), the duration of symptoms in group I prior to hospital investigation varied from six weeks to eighteen months, with an average of 6.9 months. In group II the average was 40 months. Only three cases of nineteen in which the date of onset of symptoms could be ascertained had been ill less than nine months. Four cases had been ill from ten months to two years and twelve cases had symptoms for more than two years. Thus the interval from onset of symptoms to medical study is significantly less in the cases of sprue secondary to lymphosarcoma and lends a clue to the seriousness of the underlying disease process.

The physical findings were quite similar in the two groups. Both showed marked wasting, abdominal distention, hypotension, signs of hypovitaminosis and hypocalcemia. In a few cases in each group clubbing of the fingers was noted. Lymphadenopathy and hepatosplenomegaly were absent in both groups except for two cases of Fairley and Mackie with peripheral adenopathy (No. 3 and 4, Table I). In one case a skin nodule was found on biopsy to be a lymphosarcoma.

TABLE II

AVERAGE OF MAJOR FINDINGS IN IDIOPATHIC NON-TROPICAL SPRUE PATIENTS

No. Cases	Average Age	Sex Ratio M:F	Duration of Sx to Medical Study (mo.)	Duration Life from Onset of Symptoms	Response to Therapy	% Fat of Dried Stool	Oral Glucose Tolerance	Calcium mg./100 cc. Serum	Small Bowel X-ray	Type Anemia and Color Index	Tongue Symptoms + Signs
20	45.5	¼	40	*Living* 13–75; 3 mo. *Dead* *1–60 mo. †1–41 mo.	Varied; usually fair, occasionally striking	Abnormally elevated	Low to flat	Depressed, often severely	Deficiency pattern	Hypochromic or normochromic with C.I. 1.0 or less	Usually absent

* Died of malnutrition + infection; P.M. showed no cause for sprue.
† Died elsewhere, cause unknown.

The cardinal laboratory features of steatorrhea, hypocalcemia and "deficiency" pattern on small bowel x-ray were found in practically all patients; however, the oral glucose tolerance test was normal in three of twelve patients in the "lymphoma" group but was flat to low in all cases with the "idiopathic" disease. Anemia was common to both groups. When present it was predominantly of the hypochromic variety in group II, of which only three of twenty had the macrocytic type. In group I six of sixteen cases had a color index greater than one.

The usual therapeutic measures produced improvement in patients of both groups. Surprisingly, there was a good temporary response in seven of seventeen cases in the "lymphoma" group; these patients gained weight and had increase of appetite with diminution of diarrhea. The longest remission of symptoms lasted eleven months (Case II). The response to therapy in the "idiopathic" group was variable but on the whole was more consistent and more lasting than in group I.

Of the seventeen patients in group I follow-up information is available on fifteen; all are dead. The length of time from onset of symptoms to death varied from three to twenty-nine months with an average of 12.9 months.

In the "idiopathic" group five cases of twenty are lost to follow-up; one case died a few months after the onset of the disease with no discernible

cause of steatorrhea found at autopsy, and another died elsewhere. Of the remaining thirteen one has been followed six months, one twelve months and the remainder for periods of from one to ten years, the average follow-up of all cases being 3.3 years.

The diagnosis could be made only in the "lymphoma" cases by complications which led to laparotomy or death, except for the two cases of Fairley and Mackie cited above. Of the fifteen patients in this group known to have died there was massive hemorrhage in two, intestinal obstruction in four and perforation of the bowel in three. No such complications appeared in the "idiopathic" group.

In group I "lymphogranulomatosis" of the small bowel and mesentery occurred in four instances; lymphosarcoma in six, Hodgkin's disease in two, "lymphoma" in one and giant follicle cell lymphoma in one. The duodenum was involved exclusively in one instance, the jejunum in four and the jejuno-ileum in nine. In three cases (No. 2, 3 and 4, Table 1) no biopsy material from the bowel or mesentery was available.

It can be readily seen that the differentiation of idiopathic non-tropical sprue from symptomatic sprue due to lymphoblastoma is difficult. The short duration of symptoms along with their severity is unreliable as a criterion, as any patient with the idiopathic variety may present himself early in his disease. Also, the short total course is significant only in retrospect and hence is of little benefit to the patient. Review of our series and of the literature indicates that secondary sprue may not be differentiated from idiopathic sprue by the type of anemia. We have found that sore tongue is present in symptomatic sprue as well as in the idiopathic variety. Finally, a favorable response to therapy does not rule out sprue secondary to lymphoblastoma of the gastrointestinal tract. In seven cases of sixteen suitable for analysis there was good response to therapy, lasting up to eleven months.

According to the literature, the association of sprue and lymphosarcoma of the small intestine is exceedingly rare. Inspection of collected series of lymphosarcoma of the small bowel revealed no description of the sprue syndrome; yet our cases were in many respects typical of the disease. The development of intestinal obstruction in four of seventeen cases necessitating surgery was in accord with previous descriptions of the clinical course of the disease.[10,14,27,28] Perforation and hemorrhage occur in lymphosarcoma of the small bowel, although rarely;[7,14,15,21,28] the occurrence of the former in three cases and of the latter in two cases of seventeen is somewhat unusual. The average time in lymphosarcoma of the intestine from onset of symptoms to medical study is described as between five to twenty-one months;[9,10,27,28] the average in our series was 6.3 months. Death occurred in this collected series on an average of 13.0 months after onset of symptoms, a period quite similar to that of lymphosarcoma of bowel without secondary sprue.[8,28]

In reviewing our own hospital's experience with lymphoblastoma of the small bowel from 1932 to 1952 we find that there have been sixteen cases and of these four, or 25 per cent, had symptoms of the sprue syndrome. While we are not suggesting that lymphoblastoma of the small bowel and mesentery is a common cause of the sprue syndrome, we would doubt that the association is as rare as indicated in the literature. From another standpoint we find that of twenty-five cases of non-tropical sprue, four, or nearly 20 per cent, are secondary to lymphoblastoma of the small bowel and mesentery.

SUMMARY

A survey of the literature has yielded thirteen cases of sprue secondary to histologically proven lymphoblastoma of the small intestine and mesenteric nodes. We present here four additional cases verified at operation and/or autopsy. The tumor was identified as lymphosarcoma in two instances, as reticulum-cell sarcoma in the third, and as giant follicle lymphoma (Brill-Symmers) in the fourth.

These four cases constituted 25 per cent of all cases of lymphosarcoma of the small intestine seen at our hospital over a twenty-year period, and 16 per cent of all cases of non-tropical sprue. In view of the rarity of both diseases the association is a striking one, and we suggest that lymphoblastoma of the small intestine be considered in the differential diagnosis of the sprue syndrome.

Comparison of these cases with a series of twenty cases of idiopathic non-tropical sprue revealed that the average duration of symptoms was 6.9 months in the lymphoma group and 40.0 months in the "idiopathic" group. Otherwise, no differences were observed in the history, the physical or roentgenologic findings, the laboratory data or the short-term response to

nutritive therapy. Consequently, we doubt that the diagnosis of sprue due to lymphoblastoma of the small bowel can be made before obstruction or perforation of the bowel or dissemination of the disease.

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Cardiovascular Action of 1,1-Dimethyl-4-Phenylpiperazinium Iodide (DMPP)*

A Ganglion Stimulating Agent Useful in the Diagnosis of Pheochromocytoma

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CHEN, Portman and Wickel[1] have reported that an onium compound, 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP), elevates arterial pressure and increases urinary bladder tension by stimulating autonomic ganglia.

The present study was designed to measure some of the effects of DMPP on the cardiovascular system in both laboratory animals and man and to strengthen the evidence that the drug's primary site of action is at the ganglion. The contribution of various portions of the nervous system, the adrenals and liver in the body's response to DMPP has been determined. Various chemical blocking agents were found to modify the response. The action of DMPP in neurogenic hypertensive dogs was compared with that in normotensive animals and the drug's action on a perfused denervated vascular bed was determined.

Because of its strong and selective action on ganglia, DMPP was considered worthy of clinical trial as a test for pheochromocytoma. It proved effective and a case is reported in which DMPP aided in establishing the diagnosis, proved at operation.

METHODS

Pressor-depressor responsiveness to intravenous test drugs was recorded on a revolving smoked drum from a mercury manometer after cannulation of the femoral artery. Heparin was used in the connecting tubing. Anesthesia was sodium pentobarbital (32 mg./kg.). Surgical procedures were done under sterile conditions.

To perfuse the dog's leg the proximal end of the external iliac artery was cannulated close to its origin from the aorta and blood passed through a roller-type constant output pump and returned to the distal end of the cannulated external iliac artery. The aorta was tied just below the origin of the external iliac arteries and denervation followed section of the sciatic and femoral nerves.

RESULTS

Action on Arterial Pressure of Dogs, Cats and Rabbits (Table 1). In doses of from 0.1 to 2.0 mg. DMPP elicited brief apnea and quick transient fall in arterial pressure associated with bradycardia in pentobarbitalized dogs and cats. These effects were followed by a sharp rise in pressure and increase in both rate and depth of respiration. Micturition and defecation often occurred. The sharp pressor response was followed by a slower and more sustained one with widening of pulse pressure and cardioacceleration. Intravenous doses of 0.5 mg. in dogs usually elevated arterial pressure 100 or more mm. Hg. But given intramuscularly in doses of 0.5 mg. DMPP failed to affect either respiration or arterial pressure over thirty-minute periods of observation.

Pressor responses were usually unchanged when large doses of DMPP were given repeatedly to dogs. Sometimes there was slight

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TABLE 1

EXAMPLES OF VASCULAR RESPONSIVENESS TO DMPP IN DOGS UNDER VARIOUS CONDITIONS

Condition	Dose (mg.)	Control B.P. (mm. Hg)	Response (mm. Hg)	Condition	Dose (mg.)	Control B.P. (mm. Hg)	Response (mm. Hg)
Normal	2.0	61	169	Paravertebral	0.1	144	24
	0.5	184	114	sympathectomy (A)	0.5	142	140
	1.0	110	156	and after			
	0.5	175	97	adrenalectomy			
	0.5	177	104	(B) acute	0.1	104	0
	0.5	169	62		0.5	117	85
	0.5	157	93	(B) chronic	0.1	106	0
	0.5	160	118		0.5	97	61
	0.5	190	56	(A)	0.1	124	59
	0.5	208	80		0.5	112	186
	0.25	137	69	(B) acute	0.1	99	−6 +5
	0.1	136	45		0.5	95	44
	0.25	172	32	Perfused dog's leg	0.05		+3 −8
Paravertebral	0.5	107	177		0.1		+6
sympathectomy	0.5	122	112	Perfused kidney	0.5	160	+102 −46
	0.5	132	113		0.5	154	226
	0.5	88	123		0.1	46	82
	0.5	153	116		0.05	134	76
Neurogenic hypertensive	0.5	133	37		0.05	144	>250
	1.0	119	81	Cord section at C_6	0.05	60	160
	0.5	134	44		0.2	110	−56 +100
	0.5*	160	118	Before nephrectomy	0.25		7
	0.5†	183	115	After nephrectomy	0.25		81
	0.5*	190	56				
	0.5†	219	80				
	0.5*	208	80				
	0.5†	211	78				

Effect on DMPP Responses of Cutting Vagus and Carotid Sinus Nerves

Group 1				*Group 2*			
Normal		After Vagus Section		After Vagus Section		After Section Carotid Sinus Nerve	
Control B.P. (mm. Hg)	Response (mm. Hg)	Control B.P. (mm. Hg)	Response (mm. Hg)	Control B.P. (mm. Hg)	Response (mm. Hg)	Control B.P. (mm. Hg)	Response (mm. Hg)
156	31	104	45	174	102	189	+93, −114
158	29	105	47			154	+90, −79
181	95	176	99	156	85	172	+81, −96
169	62	169	79			137	+111, −63
122	27	124	29	153	44	198	51
						153	65
				131	30	178	35
				154	42	184	55
				158	20	165	43

* Control.
† Hypertension.

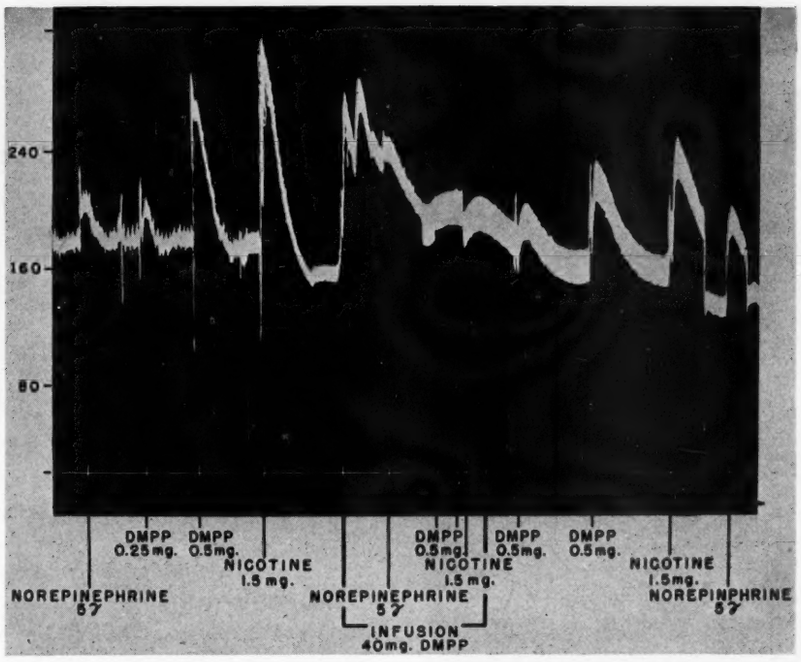

FIG. 1. Infusion of DMPP in normal dog without production of sustained hypertension. Rapid recovery of response to nicotine and DMPP with completion of infusion.

diminution of response but this was neither a constant nor an impressive finding, especially when compared with the prompt reduction in response to nicotine administered similarly. On the other hand, refractoriness developed when a large amount of DMPP was infused. With start of the infusion arterial pressure rose to great heights but then fell progressively to plateaus variously at, above or below control levels. As much as 60 mg. of DMPP infused within fifteen minutes produced only an initial hypertension followed by progressive fall in arterial pressure. Late during the infusion, and concurrently with the depressor effect, superimposed injection of 0.5 mg. of DMPP produced no response and injection of 1 or 2 mg. of nicotine produced either no response or an entirely depressor one. Refractoriness developed more slowly to DMPP than to nicotine and was less enduring. Figure 1 shows the rapidity with which refractoriness was lost and response to single injections of DMPP became pressor again.

During the brief hypertension due to infusion of DMPP vascular reactivity to nor-epinephrine was reduced; with appearance of a depressor response to infusion of DMPP, response to nor-epinephrine was augmented.

When DMPP was injected into the right atrium of the heart the systemic arterial pressure response was the same, or slightly less, than when injected directly into the arch of the aorta through a catheter inserted into a carotid artery.

In rabbits response to DMPP was similar to that in dogs and cats but sensitivity to the drug was much less. Nicotine, on the other hand, often produced an entirely depressor response, or an initial deep depressor response followed by a small after-rise in pressure. Vagus section or atropine did not prevent nicotine-induced hypotension in rabbits but small doses of TEAC, insufficient to prevent pressor responses to DMPP, caused nicotine responses to become pressor when they were initially depressor.

Action on Arterial Pressure in Man. A Peterson catheter was inserted through a 21-gauge needle into a brachial artery and arterial pressure was recorded continuously with a capacitance manometer and ink oscillograph. Drugs were injected into an antecubital vein through a polyethylene catheter.

DMPP produced responses in man similar to those in cats and dogs. (Fig. 2.) An initial transient bradycardia and fall in arterial pressure preceded a sharp rise followed by a more

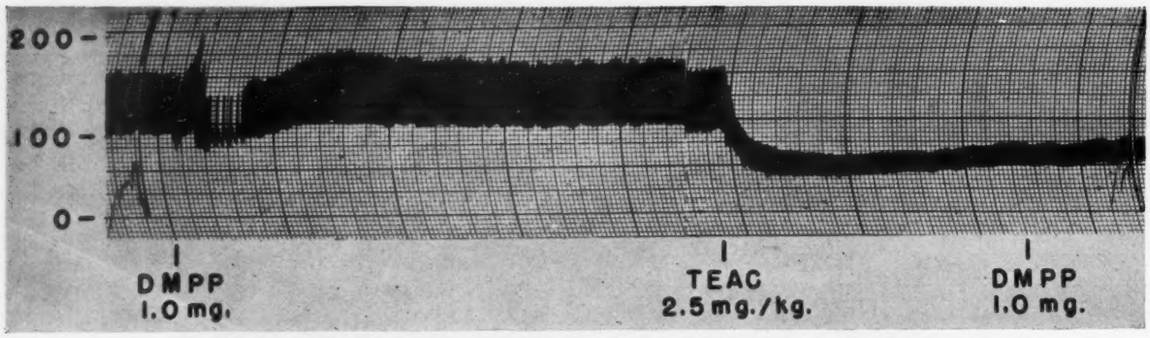

FIG. 2. Response to DMPP in patient with essential hypertension and its blockade by TEAC.

sustained pressor response. Respiratory stimulation was also similar: following an initial brief apnea both rate and depth of respiratory movements increased.

In a patient with long-standing severe hypertension whose clinical history suggested the presence of pheochromocytoma, 1.0 mg. of DMPP given intravenously caused arterial pressure to rise from a control level of 210/135 mm. Hg to 280/200 mm. Hg. Ten mg. of piperoxan hydrochloride (benodaine®) given at the height of the pressor response caused a fall in pressure to 120/70 mm. Hg. Following surgical removal of a large pheochromocytoma the same dose of DMPP produced a pressor response of only 15/2 mm. Hg from a control value of 130/90 mm. Hg. Atropine (0.8 mg.) eliminated the initial parasympathomimetic effect of the drug and did not interfere with the test.

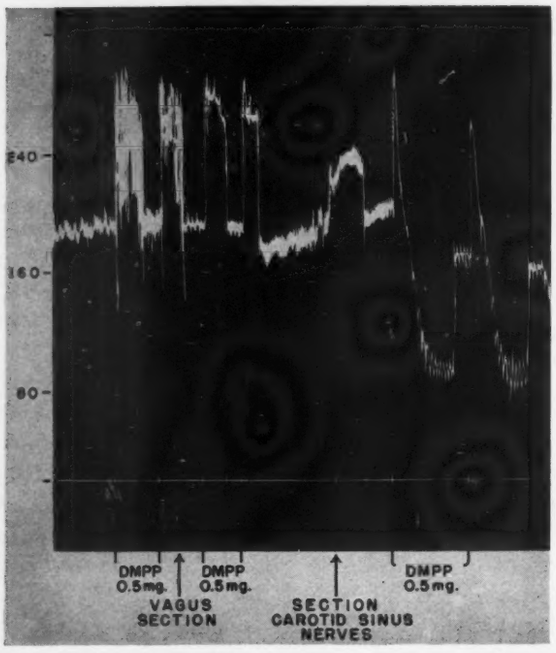

FIG. 3. Elimination of initial depressor effect of DMPP by vagus section and change in character of response after section of the carotid sinus nerves.

Effect of Cutting the Vagus and Carotid Sinus Nerves. Either atropine or section in the neck of the vagus-sympathetic-depressor trunks eliminated or greatly reduced the initial depressor response to DMPP in dogs and cats; these procedures did not prevent the respiratory stimulant action of DMPP. Sometimes the pressor action of DMPP was enhanced by vagus section, possibly by eliminating the opposing vagus mediated depressor effect; more often there was no major change in magnitude of pressor response before and after vagus section.

When section of the carotid sinus nerves followed cutting of the vagus nerves, a marked change in the character of the response often occurred. With conclusion of the hypertensive response to buffer nerve section the late pressor effect of DMPP was replaced by a sustained depressor action. (Fig. 3.) This was not invariable; in some experiments responses remained entirely pressor. The respiratory effect of large doses of DMPP was largely unchanged by buffer nerve section. But with small doses (0.005 mg.) just sufficient to produce a small initial rise in arterial pressure and brief respiratory stimulation, section of the buffer nerves reduced or eliminated respiratory stimulation without affecting, or increasing slightly, the pressor response.

Effect of Spinal Cord Section at C_6. As has been shown by Page and Taylor[2] vagus tone may be increased greatly by minor stimuli in dogs following cord section at C_6. Such was the case here also. After section of the spinal cord at C_6, with or without removal of the distal portion, DMPP often produced entirely depressor responses accompanied by marked bradycardia.

After section of the vagus nerves, DMPP produced pressor responses generally larger and more sustained than in normal dogs.

Effect of Paravertebral Sympathectomy. Bilateral removal of the paravertebral sympathetic chains from T1 to L5 one or more weeks prior to testing moderately augmented the pressor effect of DMPP.

Effect of Bilateral Adrenalectomy, Both Singly and Combined with Paravertebral Sympathectomy. When performed in normal dogs several hours before testing, bilateral adrenalectomy reduced but did not abolish the vasopressor effect of DMPP; the same procedure did not affect significantly responsiveness to nor-epinephrine. Doses of 0.5 or 1.0 mg. of DMPP produced only 30 to 60 mm. Hg rises in arterial pressure and a dose of 0.1 mg. elicited almost no change. The same results were obtained in other experiments when adrenalectomy was performed several days prior to testing and animals maintained with adrenal cortex extract to allow complete recovery from surgery.

In both acute and chronic experiments on sympathectomized dogs, adrenalectomy had the same effect on responsiveness to DMPP as in normal dogs.

Effect of Hepatectomy. Hepatectomy was done in one stage according to the method described by Firor and Stinson.[3] This procedure reduced but did not abolish the pressor action of DMPP, without affecting markedly response to nor-epinephrine.

Effect of Autonomic Blocking Agents. Chen, Portman and Wickel[1] found that both TEAC and C-6 prevent the pressor action of DMPP and Haggart and Woods[4] found responses blocked by TEAC.

In these experiments 10 to 30 mg./kg. of TEAC only moderately reduced the pressor effect of a large dose of DMPP (0.5 mg.) but smaller amounts of TEAC would prevent the pressor response to the smaller doses of DMPP used by the above authors. Hexamethonium bromide (C-6) was more effective than TEAC but doses of 1 or 2 mg./kg. blocked the pressor response to 0.5 mg. of DMPP completely in only one experiment. (Fig. 4.)

Apparently TEAC is more effective in preventing the pressor effect of DMPP in human beings than in dogs. In one patient with essential hypertension 2.5 mg./kg. of TEAC completely blocked the pressor response to DMPP. (Fig. 2.) The same dose of TEAC also reduced the intensity of the response to DMPP in a patient with pheochromocytoma.

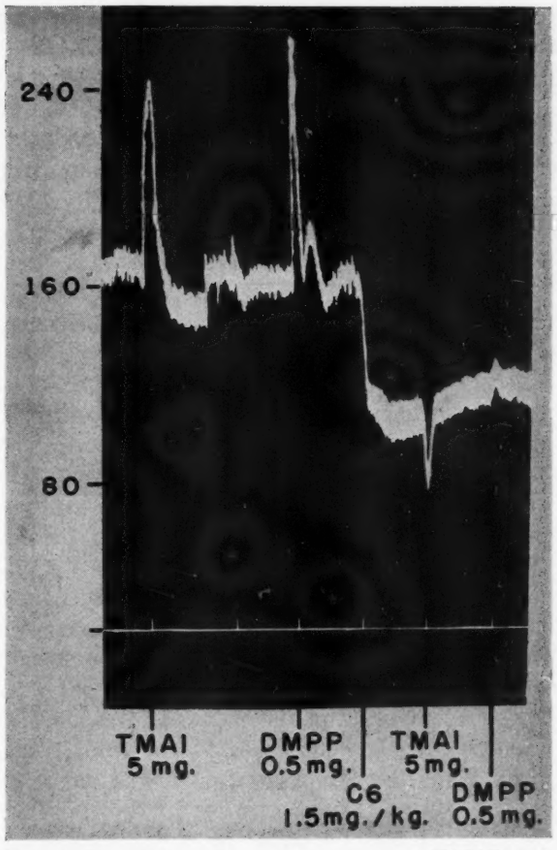

FIG. 4. Prevention of pressor response to TMAI and DMPP by C-6.

When given by infusion or in rapidly repeated injections nicotine reduced or abolished response to DMPP simultaneously with disappearance of its own pressor action.

Effect of Adrenergic Blocking Agents. 2-Benzyl-imidazoline hydrochloride (priscoline®) and 2(N-p'-tolyl-N-m-hydroxyphenyl amino methyl) imidazoline (regitine®) were given separately in amounts that reduced or reversed the pressor action of 10 μg. of nor-epinephrine. Inhibition of response to DMPP correlated with the degree to which nor-epinephrine response was suppressed; when the latter was entirely reversed the pressor action of DMPP was abolished. Repeated large doses of DMPP opposed adrenergic blockade induced by priscoline with some return of the pressor action of both nor-epinephrine and DMPP. (Table II.)

6-Allyl-6,7-dihydro-5H-dibenz(c,e) azepine phosphate (RO 2-3248)®, described by Randall and Smith[5] as an adrenergic blocking agent, was given in doses as large as 6 mg./kg. with

reduction but without completely blocking responses either to nor-epinephrine or DMPP.

Comparison of Pressor Action of DMPP with That of Tetramethylammonium Iodide (TMAI) and Nicotine. Both TMAI and nicotine produced respiratory stimulation and elicited vasopressor responses similar to those of DMPP in dogs and cats. DMPP had from ten to twenty times the pressor action of TMAI and approximately two to four times that of nicotine. As noted previously, nicotine was often entirely depressor in rabbits but TMAI and DMPP both elicited pressor responses.

TABLE II

EFFECT OF GANGLION BLOCKING AGENTS ON DMPP RESPONSES

Control Values				After Blockade	
Dose DMPP (mg.)	B.P. (mm. Hg)	Pressor Response	Agents	B.P. (mm. Hg)	Pressor Response
			TEAC		
0.5	134	44	10 mg./kg.	93	29
0.5	107	177	5 mg./kg.	100	167
0.5	122	112	10 mg./kg.		62
0.5	132	113	10 mg./kg.	113	99
0.5	86	123	5 mg./kg.	75	141
0.5	153	116	30 mg./kg.	111	50
0.5	188	70	20 mg./kg.	84	44
0.5	138	107	5 mg./kg.	79	35
			C 6		
0.25	180	43	2 mg./kg.	62	16
0.25	105	47	1.5 mg./kg.	49	0
0.5*	113	99	1 mg./kg.	105	19
0.5*	75	141		71	44
0.5*	111	50	2 mg./kg.	108	16
0.5	108	133	1.5 mg./kg.	73	29
0.5	111	123	2 mg./kg.	68	36
0.5	150	94	1 mg./kg.	106	6
			RO 3-0484		
0.5	148	100	1.5 mg./kg.	83	44
0.5	137	111	2 mg./kg.	61	53

EFFECT OF ADRENERGIC BLOCKING AGENTS ON DMPP RESPONSES

			Priscoline		
0.5	121	89	5 mg./kg.	132	+28 −23
0.5	134	102	10 mg./kg.	103	+11 −19
			Regitine		
0.2	187	36	2 mg./kg.	79	+3 −18
0.5	135	70	3 mg./kg.	100	+19 −22
			RO 2-3248		
2.0	61	169	6 mg./kg.	56	80
0.5	133	37	1 mg./kg.	70	36
0.5	184	114	2 mg./kg.	170	42

* Signifies previous blockade with TEAC

Action of DMPP on Perfused Dog's Leg. DMPP had a negligible action on the blood vessels of the perfused denervated dog's leg but when the drug reached the dog's body to stimulate the adrenal medullas and sympathetic tissue, severe vasoconstriction in the leg vessels occurred, presumably from release of epinephrine and nor-epinephrine into the circulation.

Response in Neurogenic Hypertensive Dogs. Chronic hypertension (200–260 mm. Hg) was produced by section of the carotid sinus and aortic depressor buffer nerves. The initial depressor effect of DMPP occurred in these animals just as in normal ones and was abolished by atropine. There was no significant difference between pressor responses to DMPP before and after the appearance of chronic hypertension. The marked secondary depressor action of DMPP occasionally observed after acute section of the buffer nerves was not seen in these animals with chronic neurogenic hypertension. Respiratory stimulation followed large doses of DMPP.

COMMENTS

These experiments afford confirmatory evidence that DMPP is a strong ganglion stimulating agent, as indicated by Chen, Portman and Wickel.[1] It is more powerful and has less paralyzing action than nicotine. As such, it should earn a place in both laboratory and clinical investigation.

Vascular response to an intravenous injection is characteristically triphasic in dogs, cats, rabbits and man. An initial transient bradycardia and fall in blood pressure was diminished or abolished by atropine or section of the vagus nerves. Occasionally some cardiac slowing and fall in pressure persisted after vagus section, presumably from stimulation of peripheral parasympathetic ganglia; it was not a mere peripheral action of DMPP since it was further reduced or eliminated by ganglion blocking agents. A sharp and brief pressor response followed the initial parasympathetic effect and merged into or was followed in turn by a slower and more sustained pressor response of the same, lesser or greater magnitude.

The vasopressor response to DMPP is the result of several actions: (1) stimulation of peripheral sympathetic ganglia, with vasoconstriction and cardioacceleration; (2) stimulation

of adrenal glands to release epinephrine and nor-epinephrine[6–8]—release of these amines from the adrenal glands probably depends upon both direct and reflex stimulation as occurs with nicotine;[9] (3) presumably, as with large doses of nicotine[10] there is stimulation of central vasomotor centers; (4) the liver may also release epinephrine or nor-epinephrine to contribute to the response, since hepatectomy reduced response to DMPP before affecting that to nor-epinephrine.

Vasoconstriction following intravenous injection of DMPP did not depend upon a direct action of the drug on the vessel wall, at least in the denervated vascular bed of the perfused leg. Probably it has little direct action on other vascular beds, too, since ganglion blockade inhibited or prevented the response. Lack of direct effect of DMPP in the perfused leg suggests that sympathetic nerves mediating vasoconstriction in the leg are all postganglionic.

Heymans, Bouckaert and Régniers[11] found that the pressor response to nicotine depends in part upon stimulation of carotid and aortic chemoreceptors. DMPP apparently differs from nicotine in this respect, for section of the chemoreceptor nervous pathways increased, or did not alter, pressor response to small doses of the drug. But respiratory stimulation by small doses of DMPP was reduced by elimination of chemoreceptor function and accords with the experience of Heymans et al.[11] with nicotine. With larger doses of DMPP respiratory stimulation was not appreciably modified by either acute or chronic section of the buffer nerves.

With larger doses of DMPP section of the buffer nerves often changed the character of the response. Although it was not a regular occurrence, the late sustained pressor action of DMPP was replaced by a deep, prolonged depressor response. With increased sympathetic nervous activity following section of the buffer nerves[12] the ganglion blocking action of DMPP may be more apparent, as it is with TEAC,[13] and account for the fall in pressure. But similar results were not obtained in dogs with chronic neurogenic hypertension consequent to buffer nerve section. Here pressor response to DMPP was essentially unchanged; ganglia were still capable of responding normally to stimulation despite the supposed ganglion hyperactivity which had resulted in hypertension. We have no explanation for the difference in response to DMPP in acute versus chronic neurogenic hypertension following section of the buffer nerves. But this finding may be added to the other evidence[14] that the mechanisms of the two forms of hypertension are different.

Removal of the paravertebral sympathetic chains increased rather than reduced response to DMPP. This result is presumably due to stimulation by DMPP of ganglia not removed by surgery—the celiac, mesenteric, aortic, etc.—and direct stimulation of the adrenal medulla to release epinephrine and nor-epinephrine, responsiveness to which is augmented.[2] Since augmentation to epinephrine and nor-epinephrine also occurs after vagus section and cord section at C_6, it is consistent that responses to DMPP were increased in these preparations, too.

Page and Taylor[2] found that very minor stimuli to the carotid sinus may greatly increase vagus tone after the spinal cord has been sectioned at C_6, an effect multiplied many times over responses to the same stimulus in normal dogs and one often fatal unless the vagus nerves were sectioned immediately. The effect of parasympathetic stimulation by DMPP was also much greater in cord-sectioned dogs. Responses were often entirely depressor, well illustrating the parasympathetic opposing action to the pressor response to DMPP. When injections were repeated after vagus section, the usual large pressor response developed.

DMPP produced responses of similar contour in dogs, cats, rabbits and man. In rabbits sensitivity to the drug was less but responses were pressor, contrasting with those to nicotine which, as has been observed[15] were depressor both before and after section of the vagus nerves. This action of nicotine in rabbits may depend upon the drug's greater ability to paralyze sympathetic ganglia in this species. If small doses of TEAC were given, doses insufficient to block the pressor action of DMPP, further blockade by nicotine was reduced so that ganglion stimulation predominated to produce entirely pressor responses.

Since piperidine has been shown by von Euler[16] to be present in human urine in amounts up to 10 mg./L., it would be surprising if the related piperazinium compounds also were not found in mammals. Diketopiperazine is among the products of fermentative hydrolysis of proteins and it, along with the dihydroxy derivative, is formed from amino acids and dipeptides. The secondary amine, piperazine, is a strong base.

Piperidine and its propyl derivative, conine, have been shown by Koppanyi[17] to have an initial ganglion-stimulating action followed by nicotine-like paralysis. With paralysis there was augmentation of the pressor action of epinephrine; augmentation was much less, however, than that found by Page and Taylor[2] with TEAC.

DMPP may prove useful clinically as a test for the presence of pheochromocytoma. It should more effectively precipitate a "crisis" than either histamine, TEAC or mecholyl® because of its stronger and more specific action on ganglia and adrenal glands. Its use in patients should be guarded by ready availability of adrenergic blocking agents if a dangerous rise in arterial pressure occurs. If a typical pheochromocytoma "crisis" can be elicited with DMPP, injection of one of the adrenergic blocking drugs will cause marked lowering of arterial pressure. Serial use of the two drugs should be useful in establishing a diagnosis of pheochromocytoma; if an adrenergic blocking agent is used alone, and adrenalemia is slight at the time, the test may be inconclusive.

SUMMARY

1. DMPP (1,1-dimethyl-4-phenylpiperazinium iodide) stimulated sympathetic ganglia more powerfully than nicotine and tetramethylammonium iodide and had less ganglion paralyzing action than nicotine in dogs, cats, rabbits and man. It differed from nicotine also in that its vasopressor action was largely independent of carotid and aortic chemoreceptor function. Respiratory stimulation, however, depended in part upon stimulation of these chemoreceptors.

2. The pressor effect of DMPP depended upon release of epinephrine and/or norepinephrine from the adrenal glands and liver and stimulation of sympathetic ganglia with resultant vasoconstriction and cardioacceleration. The drug had no prominent direct action on blood vessels, at least in the perfused denervated dog's leg.

3. Stimulation of parasympathetic ganglia caused initial transient bradycardia and fall in blood pressure that tended to inhibit the pressor action of DMPP. This opposing action was especially prominent after spinal cord section at C_6 and was eliminated by atropine or section of the vagus nerves.

4. Section of the spinal cord at C_6 or paravertebral sympathectomy augmented the pressor action of DMPP, since these procedures also augment the pressor action of epinephrine and nor-epinephrine.

5. TEAC, nicotine and hexamethonium all inhibited the ganglion-stimulating action of DMPP. The adrenergic blocking agents, priscoline, regitine and RO 2-3248, inhibited the pressor action of DMPP to a degree directly dependent on the inhibition of pressor response to nor-epinephrine.

6. Response to DMPP was not altered by production of chronic neurogenic hypertension in dogs by section of the carotid sinus and aortic depressor nerves. But during the acute hypertension immediately following section of the buffer nerves the late sustained pressor action of DMPP was often replaced by a pronounced depressor effect. The significance of this difference is unknown, other than it may be listed with other observations suggesting that the two forms of hypertension depend on different mechanisms.

7. DMPP has proved useful in the diagnosis of pheochromocytoma because of its strong and specific action on ganglia and adrenal medullary tissue. It ensures a high secretory activity of the tumor, the effect of which is specifically inhibited by adrenergic blocking agents.

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Review

Clinical and Hematologic Effects of Triethylene Melamine*

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ENCOURAGING reports have appeared on the use of triethylene melamine (TEM) † for treatment of leukemia, lymphoblastoma and other diseases.[3,15,17,18,19,21,24,27,29,35,37,38,39,40,46,47] The history, chemistry and experimental studies of this compound have been given in detail elsewhere.[2,5–8,13,22,25,29,30,31,33] The main effects of treatment with TEM will be reviewed and summarized. Our experiences with the use of this drug in patients with conditions not previously reported in adequate detail will be presented. Table I is a summary of over 1,000 reported cases; Table II indicates cases from our material, selected because they illustrate important features.

TABLE I

SUMMARY OF CASES TREATED WITH TEM—COMPOSITE DATA FROM VARIOUS REPORTS

	Total Cases
Lymphoblastoma	
Hodgkin's disease[1,3,12,15,17,18,21,24,26,27,28,32,37,38,39,40,46,47]	350
Lymphosarcoma[3,15,18,21,22,24,26,28,29,37,38,39,40,47]	136
Follicular lymphoblastoma[27,28]	5
Reticulum cell sarcoma[3,15,18,21,24,26,27,28,36,37,38,40,46,47]	33
Acute leukemia:	
Granulocytic[3,27,28,29,38,40]	35
Lymphocytic[28,38]	13
Monocytic[3,27,39,40]	9
Undifferentiated[19,29,40]	8
Chronic granulocytic leukemia[3,21,22,24,26,27,28,29,38,39,40,47]	119
Chronic lymphocytic leukemia[3,17,19,21,24,26,27,28,37,38,39,40,46]	138
Leukosarcomatosis[21]	7
Other forms of leukemia:	
Subacute[3,27,29]	7
Panmyelosis[38]	3
Plasma cell type[27]	1
Myelomatosis[3,17,21,27,28,29,38,46]	23
Mycosis fungoides[21,27,38,39,47]	18
Polycythemia vera[27,28,35,38,39]	70
Carcinoma of the lung[15,21,24,27,38,39,46]	25
Fibrosarcoma[46,47]	4
Other miscellaneous diseases[3,15,18,21,24,27,29,38,39,46,47]	55

TABLE II

AUTHORS' CASES TREATED WITH TEM

	No.
Lymphoblastoma	
Hodgkin's disease	3
Acute leukemia	3
Chronic lymphocytic leukemia	3
Lymphosarcomatosis	1
Other forms of leukemia	
Subacute granulocytic	1
Reticuloendotheliosis	
Aleukemic	2
Acute lymphocytic	1
Di Guglielmo's disease	1
Myelomatosis	1
Mycosis fungoides	1
Nephrotic syndrome	3

GENERAL EFFECTS OF TEM

The effect of TEM on normal tissues is similar to that of the nitrogen mustards. Atrophy and necrosis of lymphoid, myeloid, hepatic, adrenal and testicular tissues has been observed.[8,22,31,33,39] Furthermore, TEM inhibits tumor growth and leukemia in animals.[5–8,25,29,39]

TEM can be given orally, intramuscularly and intravenously with little or no local or systemic reaction. Occasionally parenteral administration may result in local tissue reaction, as with nitrogen mustard.[16,21,39] Anorexia, vomiting and occasionally diarrhea occurring four to twenty-four hours after administration are infrequent immediate toxic effects,[3,15,19,21,24,27,29,31,38,39,40,46,47] which can be avoided by decreasing the daily dose of TEM,[21,27,46] by giving the drug at night or by giving 50 mg. of pyridoxine with TEM.[40,46,47] Since the symp-

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† Triethylene melamine was supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River New York.

toms also occur after intravenous administration,[21,39] they are probably not due to local irritation. Less common toxic effects are euphoria,[27] urticaria,[3] abdominal pain associated with nausea or vomiting[47] and alopecia.[28] Renal toxicity has been noted[3,21,23,24,46,47] although detailed renal function tests or tissue studies have not been recorded. Transient hematuria, albuminuria and retention of urea nitrogen have been observed and death of one patient has been attributed to this toxic effect.[3,46,47] One of our patients with chronic lymphocytic leukemia exhibited increasing retention of urea nitrogen two weeks after the onset of TEM therapy. The azotemia followed a dramatic fall in total leukocyte count from 137,000 to 17,000 per cu. mm. in seven days. Hyperuricemia with obstructive uremia rather than TEM renal toxicity is a possibility in this case.* Although hepatic necrosis has been reported in animals receiving TEM,[33] there are only three reported cases[27,28] with liver damage which could be attributed to the drug. One of our patients with acute leukemia developed icterus two weeks after the first course of TEM. There was no history of parenteral medication. He expired three weeks after receiving a total of 20 mg. of TEM. At autopsy the liver contained practically no traces of leukemic tissue but there was extreme atrophy of liver parenchyma. Serum homologous hepatitis as a cause of the atrophy could not be ruled out. We observed no significant alteration in liver function in our other patients treated with TEM.

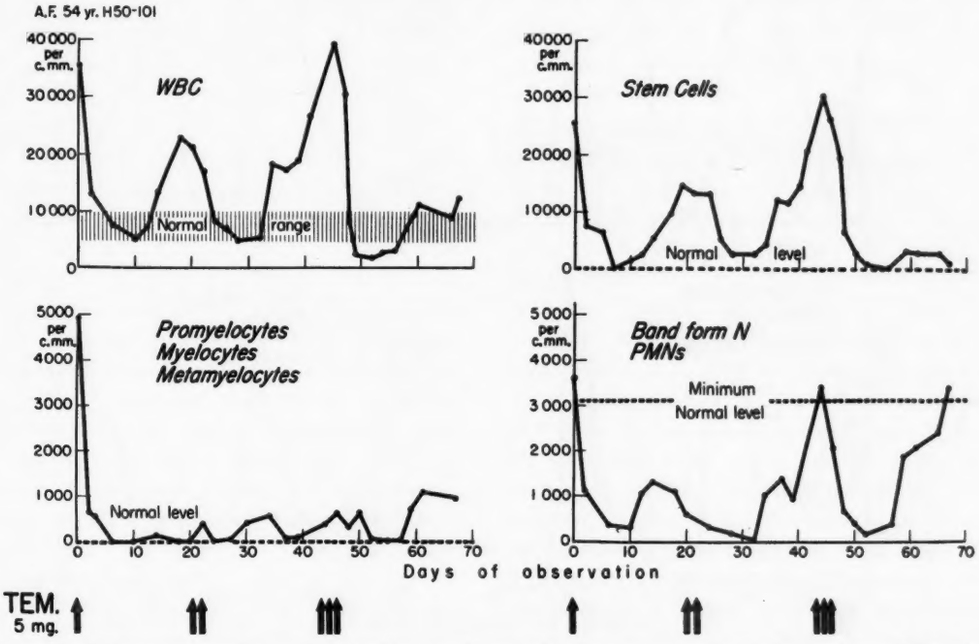

FIG. 1. Subacute granulocytic leukemia; total and absolute counts of cells in peripheral blood.

HEMATOLOGIC EFFECTS OF TEM

Effect of TEM on Leukocytes. This varies from transient and slight leukopenia to marrow aplasia and death, and is not related to the dose of TEM but rather to the type and extent of the disease and hematologic status, general condition and previous therapy of the patient.[17,21,24,26] Granulocytes and lymphocytes are decreased and eosinophilia may occur.[28,29,40] Normal or elevated initial leukocyte counts decrease significantly by the third or fourth day.[40] Lowest counts are noted between the sixth and twentieth days.[15,21,39,40,47] Occasionally an initial rise in the total count is noted prior to the decrease.[19,29]

We observed three patterns of leukocyte response to TEM in patients with normal leukocyte counts: (1) a sharp, dramatic decrease in all elements may occur; (2) an initial rise may be followed by a decrease and (3) no significant change in the leukocytes. Our patients with leukocytosis exhibited maximum decrease in the total leukocyte count from the fourth to tenth day of treatment, followed by a rise to maximum levels fifteen to twenty days later.

* Specific renal function tests on two of our patients before and after therapeutic doses of TEM revealed no evidence of renal toxicity.

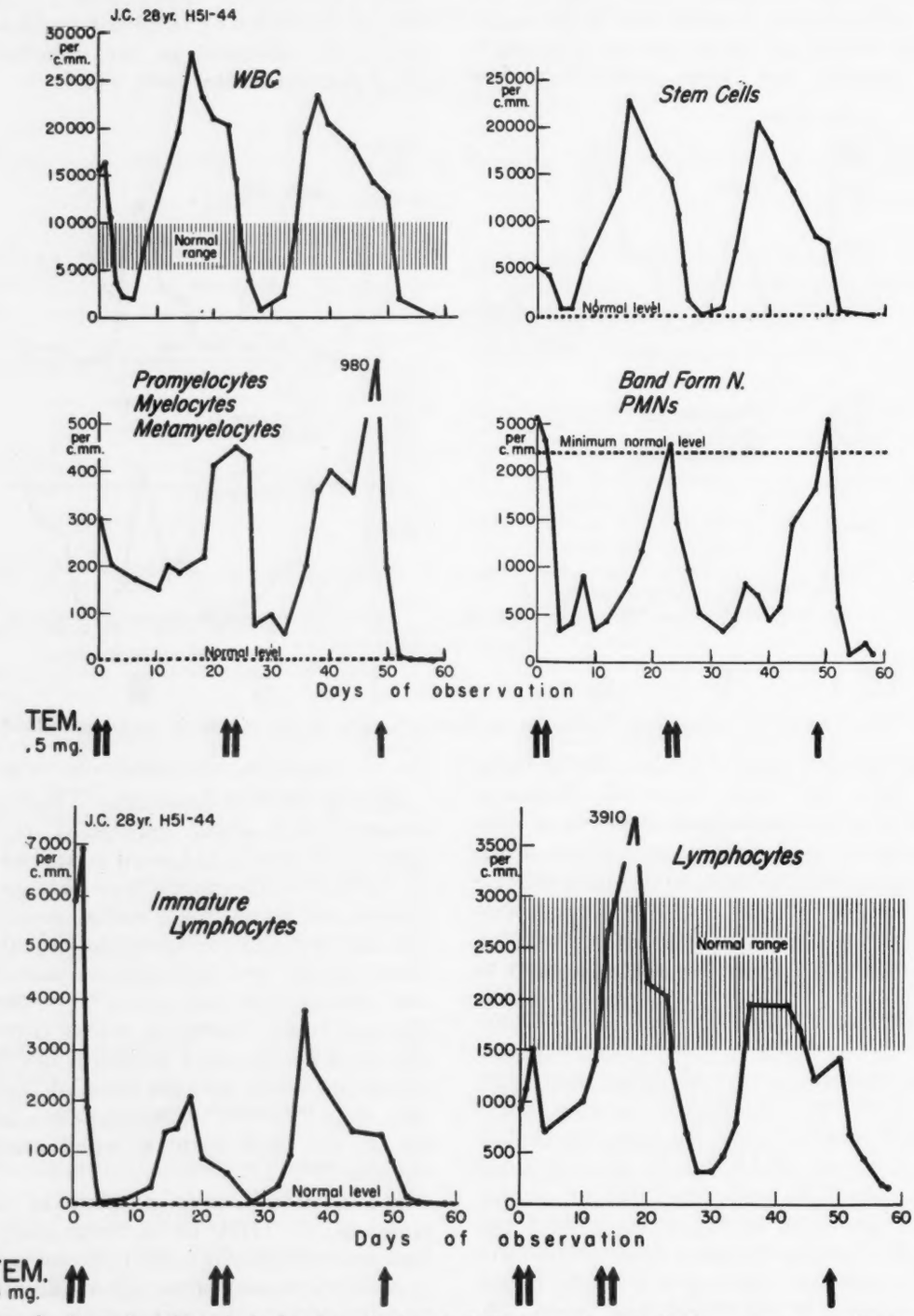

FIG. 2. Acute lymphocytic leukemic reticuloendotheliosis; total and absolute counts of cells in peripheral blood.

(Fig. 1.) Occasionally an increase in both mature and immature cells exceeding the initial counts occurs after therapy. Immature cells and mature cells are usually affected equally. (Fig. 1.) In general, the number of stem cells parallels changes in total leukocyte count. We observed no difference in sensitivity among granulocytes and lymphocytes, but initial rises and secondary rises greater than the pretreatment counts were seen more frequently in the lymphocyte series. (Fig. 2.)

Effect of TEM on Platelets and Erythrocytes. The most constant alteration in platelet and erythrocyte counts is slight decrease.[15,21,27,29,37–40,47] Occasional patients develop severe anemia and marked thrombocytopenia with bleeding as a result of marrow damage.[17,21,27,37,38,39] Frequent erythrocyte counts in our patients failed to demonstrate changes which could be attributed to the drug. Only one patient with acute leukemia developed thrombocytopenia and spontaneous hemorrhage following therapy. The number of erythroblasts in the peripheral blood of one of our patients with erythro-leukopiastrinemia (Di Guglielmo's panmyelosis) was not changed by treatment.

Effect of TEM on Bone Marrow. Temporary or permanent bone marrow damage occurs from one to three weeks after therapy.[3,17,18,21,24,26,27,28,37,39,40] The most severe effects occur in patients with far advanced disease or with previously damaged bone marrow.[20,36] Granulopoiesis and thrombopoiesis are affected first and erythropoiesis is affected only when bone marrow damage is severe.[17,18,21,40] Recovery may occur within two to six weeks[21,37,38,39] although the peripheral pancytopenia may persist as long as two to three months.[40] Bone marrow damage may occur later and continue longer after TEM therapy than after nitrogen mustards.[17] According to Karnofsky et al.[21] the toxic effects on the hematopoietic system are more severe and more prolonged after oral than after intravenous TEM therapy. In acute leukemia we observed no significant change in the bone marrow even though the peripheral stem cell counts dropped sharply as a result of therapy. In other diseases, however, bone marrow changes paralleled those in the peripheral blood.

THERAPEUTIC EFFECTS OF TEM

Lymphoblastoma. Previously untreated patients with Hodgkin's disease and those in good general condition, but with advanced disease, may experience excellent and occasionally dramatic subjective and objective improvement.[3,15,17,21,24,27,37,38,39] Occasional patients respond to TEM and not to other forms of therapy, whereas others may respond to irradiation or nitrogen mustard without responding to TEM.[3,17,28,37,39] Patients in poor general condition derive transient or no benefit, in contrast to the occasional dramatic response of such patients to nitrogen mustard.[1,10,15,21,27,37,38] The onset of remission is indicated first by subjective improvement as early as the second day but usually between the sixth and fifteenth day.[15,21,27,39,40,46] The duration of remission varies from three to twenty-four weeks.[3,17,21,24,27,37,39,40,46,47] With repeated courses of therapy, clinical response usually diminishes.[27,28] Three of our patients with Hodgkin's disease were treated with TEM. The first patient received no previous therapy and was in good general condition. She had an excellent remission lasting twenty weeks. The second patient experienced intestinal perforation due to Hodgkin's disease. Two and one-half months after surgical repair of the perforation a total of 20 mg. of TEM was given. Transient beneficial effect, lasting less than one week, occurred. The course of the third patient is shown in Figure 3. Despite previous therapy with nitrogen mustard and irradiation the patient complained of severe bone pain with unremitting fever. Three courses of nitrogen mustard therapy produced dramatic but transient clinical improvement. Even with marked increase in TEM dosage only brief clinical improvement was induced.

Most cases of lymphosarcoma experience incomplete or transient beneficial effect with TEM therapy.[3,21,22,24,28,29,37–40,47] Occasional patients exhibit excellent response to small doses of TEM.[21,39] Patients refractory to nitrogen mustard or irradiation may respond to TEM.[21] TEM has minimal or no effect on patients with reticulum cell sarcoma.[3,21,24,26,27,28,36,37,38,40,46,47] Rundles et al.[38] observed transient beneficial effect in three of seven cases of lymphocytic lymphoblastoma. Of the five cases of follicular lymphoblastoma treated with TEM, favorable clinical results were observed in two.[27,38]

In summarizing the effects of TEM in the treatment of lymphoblastomas we may state that the best clinical effects can be expected in patients with Hodgkin's disease who have not received previous therapy or those in good general condition with systemic involvement.

Improvement is usually noted between the first and second week of treatment. The degree and duration of remission are variable and unpredictable. Changes in the peripheral blood or marrow do not necessarily accompany clinical response. Incomplete or transient benefit usually occurs after TEM therapy for lymphosarcoma although occasional patients with this disease may be very sensitive to small doses of the drug. TEM has little or no effect on reticulum cell sarcoma. Occasional patients with lymphocytic lymphoblastoma or follicular lymphoblastoma may experience brief beneficial effect.

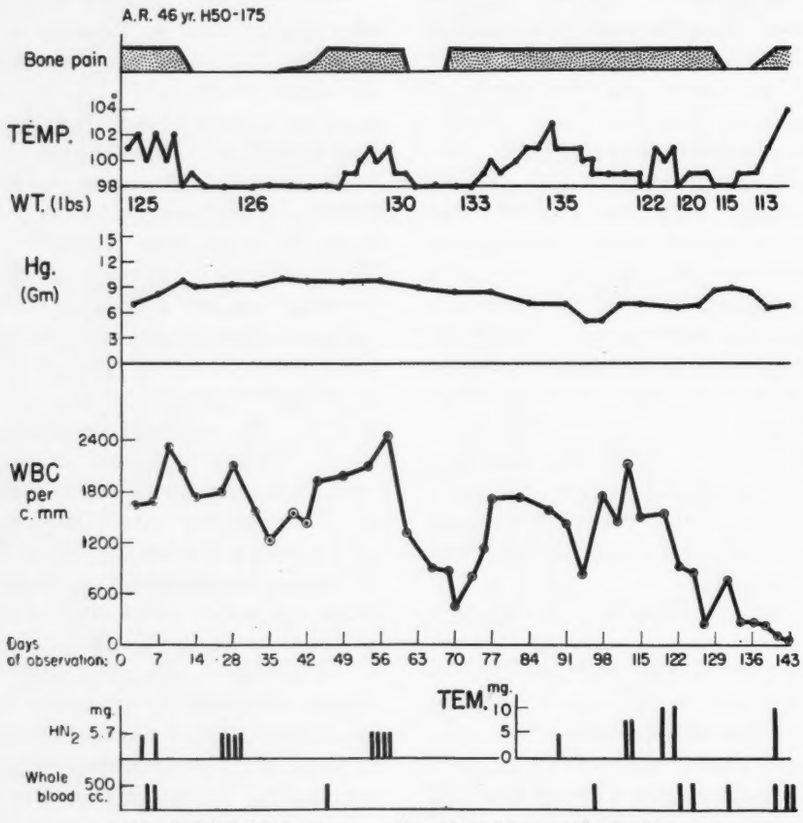

FIG. 3. Hodgkin's disease; clinical and hematologic data.

Acute Leukemia. The dramatic and prolonged remissions observed in acute leukemia after treatment with anti-folic acid compounds, ACTH or cortisone[14,34,43] have not been noted after TEM. Review of results obtained by various investigators indicates that, in general, the effects of TEM therapy are unpredictable and, at best, very transient. Some patients with the granulocytic form of acute leukemia had definite although transient clinical and hematologic remissions lasting from five days to three months.[3,27,29] Others with either acute granulocytic or lymphocytic leukemia experienced slight or no beneficial effect.[19,27,28,29,38,40] Only three of the ten patients reported with monocytic leukemia had even transient response.[3,27,39,40] In some, diminution of gum hypertrophy occurred after therapy.[28] A secondary rise in leukocytes greater than the initial count occurs in some patients after therapy is discontinued.[19] This "rebound" phenomenon is demonstrated in two of our cases. (Figs. 1 and 2.) Three of our patients with acute leukemia were treated with TEM. Two had no clinical benefit and the third patient had definite although transient beneficial effect eight days after onset of therapy. In no case was there decrease in size of the lymph nodes or spleen. The hematologic findings of one of our patients is shown in Figure 4. In only one patient was there decrease in platelets with spontaneous hemorrhage.

Chronic Granulocytic Leukemia. Over 50 per cent of the reported cases of chronic granulocytic leukemia had remissions lasting from three weeks to more than twelve months.[3,21,22,26,27,28,29,38,40,47] Clinical response was usually marked and associated with decrease in size of the liver

and spleen.[19,21,24,28,29,38,40,47] Definite clinical improvement occurred without decrease in size of the spleen[19,24] and hematologic changes were observed without clinical improvement.[3,40] Poor response to TEM did not imply poor response to other forms of therapy.[28]

Chronic Lymphocytic Leukemia and "Leukolymphosarcoma." In these disorders usually good clinical and hematologic remissions, in some

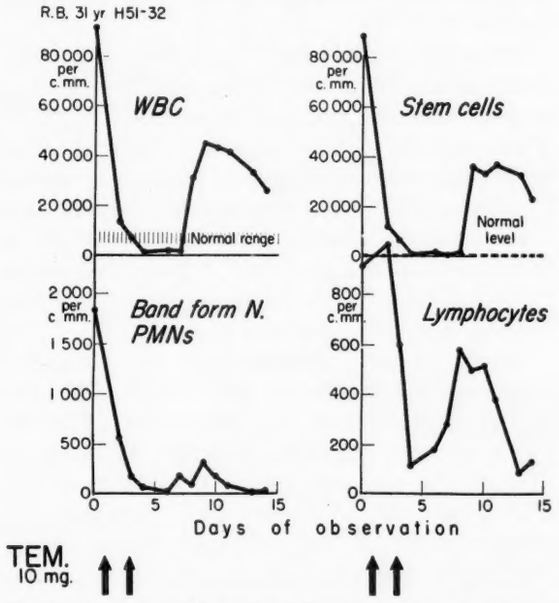

FIG. 4. Acute granulocytic leukemia; total and absolute counts of cells in peripheral blood.

cases lasting longer than fourteen months, have been observed.[3,19,21,24,26,27,28,37–40,46] TEM was of least benefit to patients with far advanced disease, particularly if marrow replacement was marked.[3,38,46] In some cases marked sensitivity was observed to even small doses[17,27,28,39] while in others prolonged therapy was necessary before significant improvement was noted.[21,24,28,46] Four of our patients with chronic lymphocytic leukemia or lymphosarcomatosis were treated with TEM. One patient had a pulmonary lesion at the right apex which was considered to be tuberculous although positive bacteriologic evidence was never obtained. The spleen decreased in size within the first week of therapy. Immediately after onset of treatment the patient developed a productive cough with increase in size of the pulmonary lesion. He expired twenty-nine days later. TEM may have activated a tuberculous lesion. A patient with chronic lymphocytic leukemia and generalized leukemia cutis and another with lymphosarcomatosis had no significant clinical or hematologic benefit from TEM therapy. The fourth patient, a forty-eight year male who had received no previous therapy, had definite hematologic response to only 5 mg. of TEM (Fig. 5) although there was no decrease in size of the lymph nodes until a total of 20 mg. of TEM was given.

Other Forms of Leukemia. Of the seven patients reported with subacute leukemia only one, with

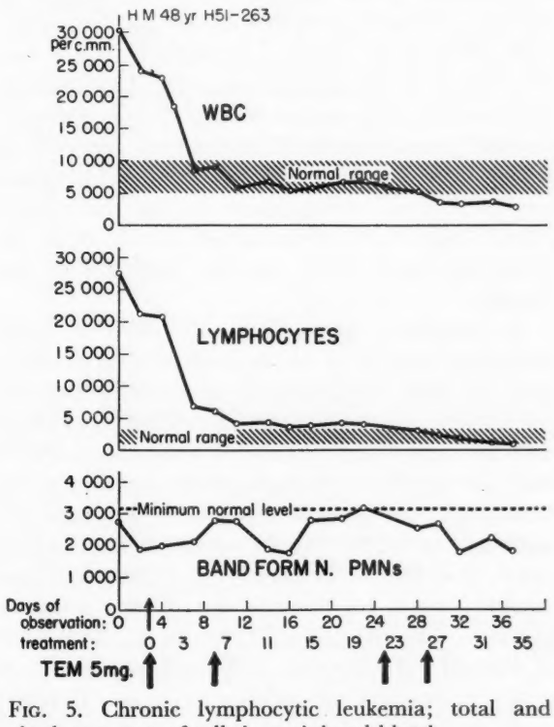

FIG. 5. Chronic lymphocytic leukemia; total and absolute counts of cells in peripheral blood.

granulocytic type had a significant remission, lasting two months.[3,27,29] One patient with plasma cell leukemia showed no response to TEM.[27] Rundles et al.[38] observed three patients with panmyelosis treated with TEM, none of whom had definite benefit. One of our patients with subacute granulocytic leukemia was treated with TEM. (Fig. 1.) Although transient hematologic remission was induced on three occasions, clinical benefit was minimal. There was no decrease in size of the liver or spleen and fever persisted. Three of our patients with reticuloendotheliosis were treated with TEM. The first patient, a forty-eight year old male, had aleukemic reticuloendotheliosis and exhibited numerous subcutaneous tumors. He received a total of 10 mg. of TEM and within three days the total leukocyte count dropped to very low levels. The size and character of the

subcutaneous tumors did not change and the patient's condition deteriorated despite therapy. The second patient with aleukemic reticuloendotheliosis had decrease in bone pain after therapy without objective change in bone lesions. The third patient had acute lymphocytic leukemic reticuloendotheliosis. (Fig. 2.) There was definite although transient clinical improvement after the first two courses of treatment. This patient demonstrated the marked increase of both mature and immature cells after each course. Terminally there was depression of all marrow elements. One patient with erythro-leuko-piastrinemia (Di Guglielmo's disease) treated with TEM had no decrease in size of liver or spleen and no significant decrease in number of normoblasts in the peripheral blood, and there was no evidence that the drug had any effect on the progress of the disease.

In summary, the effects of TEM in acute leukemia appear to be variable and unpredictable. At best, beneficial effects are transient and incomplete although remissions as long as three months have been reported occasionally. TEM may be an effective therapeutic agent for the treatment of chronic granulocytic leukemia although no effect can be expected in terminal cases. Failure to respond to TEM does not imply failure to respond to other forms of therapy. The drug is effective in the treatment of chronic lymphocytic leukemia, especially in early or moderately advanced cases. Patients may be unusually sensitive to the drug, hence small doses should be given initially. Frequently incomplete remissions are induced unless prolonged therapy is undertaken. Remissions as long as fourteen months have been observed.

Only transient hematologic and clinical improvement is to be expected in subacute leukemia and prognosis is unaffected by therapy. TEM has little effect in aleukemic and leukemic reticuloendotheliosis.

Effects of TEM in Other Diseases. An occasional patient with multiple myeloma may experience decrease in bone pain with TEM therapy although objective changes have not been reported.[3,17,21,27,28,29,38,46] One of our patients with myelomatosis had no benefit from TEM therapy.

Dramatic clearing of skin lesions with relief from pruritus may occur in some patients with mycosis fungoides but usually no benefit is noted.[21,27,38,39,47] One of our patients with mycosis fungoides had no benefit from repeated courses of TEM therapy.

Transient and rather minimal beneficial effects have been observed in patients with fibrosarcoma receiving TEM.[46,47] No effect attributable to TEM has been observed in a number of patients with osteogenic sarcoma[21,27,46,47] or other sarcomas and carcinomas.[3,17,21,27,38,39,46,47] Occasional patients with carcinoma of the lung had transient although definite clinical benefit.[15,21,24,38]

Although patients have been followed a relatively short time, the results of TEM therapy in polycythemia vera are impressive.[27,28,35,38,39] The immediate effects appear to be as good as those observed following P-32 therapy or splenic irradiation.[27,28,35,40] Satisfactory clinical and hematologic remissions have been reported for as long as fourteen months.[27,38] Patients resistant to P-32 therapy were usually resistant to TEM, even with marked increase in dosage.[27]

Three of our patients with the nephrotic syndrome were treated with TEM. The first had no diuresis after two courses of TEM but diuresed with ACTH therapy. The second patient also had no diuretic effect with TEM. The third (Fig. 6) experienced vomiting after 5 mg. of TEM but tolerated smaller doses. Diuresis occurred without significant hematologic effect. Specific renal function tests before and after TEM therapy showed a decrease in glomerular filtration rate and maximal tubular excretion of para-amino-hippurate without significant change in renal plasma flow. These studies suggest that diuresis may have occurred as a result of disturbance of renal tubular function.[20] The effect of TEM on the kidneys is probably similar to that reported with nitrogen mustard.[9,42]

CONCLUSIONS

It is apparent from a review of the literature and our own observations that TEM is a palliative and potentially toxic drug, having temporary effects. TEM apparently does not alter the course of the disease and does not appreciably prolong life. The margin between therapeutic and toxic doses in many patients is often narrow. Even though a final evaluation of the place of TEM in cancer chemotherapy cannot be made at present, certain facts are clear on the basis of present experience.

The toxic effects of TEM on both normal and malignant tissue are similar to those of nitrogen

mustard, as might be expected from the similarity in chemical structure of the active groups. In contrast to nitrogen mustard, TEM results in little or no local or systemic reaction, whether given intravenously, intramuscularly or orally. The infrequent and mild gastrointestinal reactions occur four to twenty-four hours after administration of TEM, compared with one to three hours after nitrogen mustard. TEM may result in direct renal or hepatic damage, although conclusive evidence for this is lacking at present. Hyperuricemia with subsequent obstructive uremia may result from rapid leukocyte destruction induced by TEM therapy.[11,21,39]

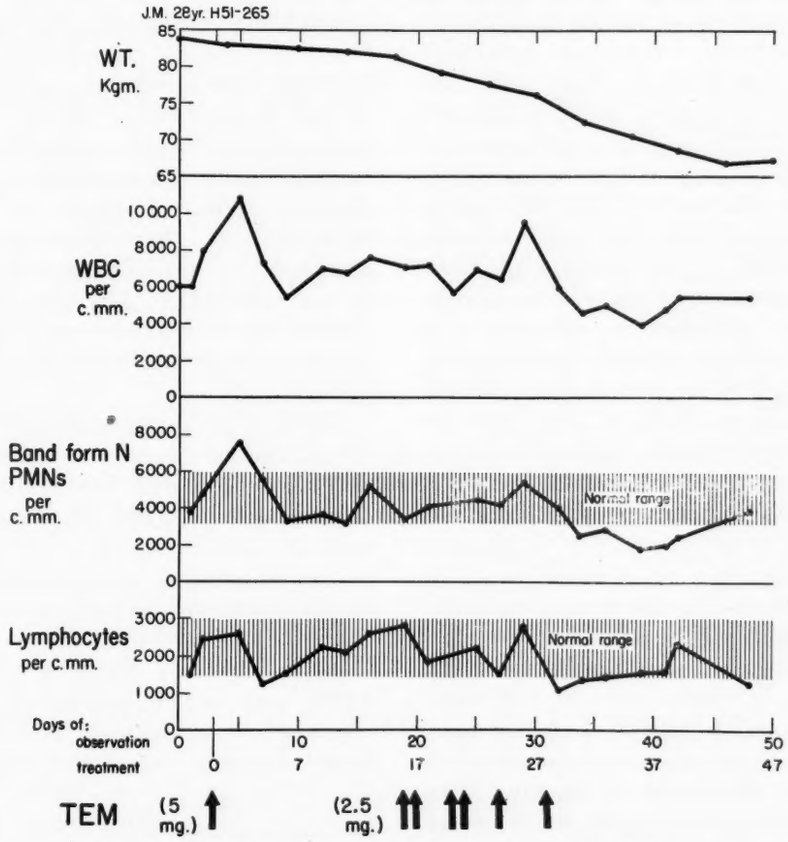

FIG. 6. Nephrotic syndrome; clinical and hematologic data.

The most pronounced effect of TEM is on the myeloid and lymphoid leukocytes. Significant decreases in total leukocyte counts may be expected by the third or fourth day after therapy, with maximum effect by the sixth to twentieth day. Occasionally secondary rises of leukocytes even greater than the initial counts are observed. We were unable to correlate this "rebound" phenomena with significant marrow changes. We observed no marked variation in the sensitivity of lymphocytes or granulocytes to TEM. Leukopenia due to marrow damage may occur after TEM therapy. We are aware of no reports of the use of L-cysteine to modify the leukopenic effects of TEM, although citrovorum factor has been effective in a few patients.[44,46,47]

Other than the rare occurrence of hemolytic anemia,[3,24,38] the effect of TEM on erythrocytes and platelets of patients with leukemia or lymphoblastoma is inconstant unless bone marrow damage is produced. Permanent bone marrow damage can be induced with TEM, as with nitrogen mustard. In general, the bone marrow changes induced by TEM parallel those in the peripheral blood, with the exception that in acute leukemia no remarkable bone marrow changes occur even though peripheral stem cell counts drop sharply as a result of therapy.

TEM has a definite place in the treatment of systemic Hodgkin's disease, particularly in patients being treated on an ambulatory basis or in whom vomiting may be deleterious. Occasionally there is a response to TEM after

failure of other forms of therapy. Subjective improvement is usually noted within the second week after TEM therapy, whereas it is noted somewhat earlier after nitrogen mustard. The degree and duration of remission is variable and probably not as complete as that following nitrogen mustard therapy.[29,39] TEM is of little value in the treatment of lymphosarcoma or reticulum cell sarcoma. Occasional cases with lymphocytic lymphoblastoma and follicular lymphoblastoma may respond to TEM therapy.

The effect of TEM in acute, subacute and reticulum forms of leukemia is minimal. It does not seem to offer as much for the patient with acute or subacute leukemia, as do the antifolic acid compounds, ACTH or cortisone. TEM can be an effective form of therapy in chronic granulocytic and lymphocytic leukemia. The drug appears to be more effective and its action is more predictable in the treatment of chronic lymphocytic leukemia than is the case for nitrogen mustard. Dramatic clinical improvement is sometimes noted without hematologic benefit. Failure to respond to TEM does not imply refractoriness to other forms of therapy. Unusual sensitivity has been noted in some patients with chronic lymphocytic leukemia; small initial doses should be used.

No remarkable effect can be attributed to TEM in its use in other types of malignant tumors. Occasional beneficial but transient results have been observed in mycosis fungoides, fibrosarcoma and carcinoma of the lung. The effectiveness of TEM in such cases needs further study.

The encouraging results of the use of TEM in polycythemia vera is to be expected from the known effects of nitrogen mustard in that disease,[41] but the number of patients followed for adequate periods is too small to determine the duration of the induced remissions.

We have used TEM to induce diuresis in patients with the nephrotic syndrome. Specific renal function tests in one case suggest that tubular damage induced by the drug resulted in decreased water resorption.

Since TEM is inactivated in the stomach by organic materials and gastric acid, it should be given to the fasting patient.[3,21,24,37,40,46] Gellhorn et al.[15] observed a more constant therapeutic effect if TEM is given with 2 gm. of sodium bicarbonate to the fasting patient. We have observed better control of both clinical and hematopoietic effects if the following therapeutic regimen is followed: A total of 5 to 10 mg. of TEM is given initially orally and not repeated for two or three weeks or until maximum effect is observed. If moderate leukopenia or other signs of marrow damage occur and clinical improvement is not observed, clinical benefit is not expected and the drug is not repeated. In general, the usual guides for therapy with other forms of cancer chemotherapy, particularly urethane and nitrogen mustard, can be applied to the therapy with TEM.[4,10,45] We suggest evaluation of bone marrow status prior to therapy. Thereafter weekly determinations of absolute leukocyte counts are probably adequate to detect the common hematologic complications. In thrombocytopenic patients platelet counts should be repeated periodically. Repeat bone marrow examinations may be necessary if severe hematologic complications occur.

TEM is particularly suited for ambulatory administration because of its ease of administration. Doses ranging from 1.0 to 5.0 mg. per week[17,38] to 5 to 30 mg. per month[21,40] have been used. If maintenance therapy is contemplated, we would suggest repeated hepatic and renal function tests in addition to peripheral blood and bone marrow studies.

When used for carefully selected patients, TEM may be an important adjunct to the physician's therapeutic aramentarium until better methods of treatment become available.

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Seminars on Neuromuscular Physiology

Abnormalities in Neuromuscular Transmission, with Special Reference to Myasthenia Gravis*

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IT is the purpose of this seminar to discuss the current state of our knowledge concerning those clinical situations which are characterized by an abnormality in the transmission of nerve impulses across the neuromuscular junction. As this is a very broad subject it has seemed best to limit ourselves to consideration of (1) a spontaneously occurring disease, myasthenia gravis; (2) a type of paralysis produced by a highly potent bacterial toxin, botulism; and (3) the effects of certain chemicals, including anticholinesterase compounds such as parathion.

MYASTHENIA GRAVIS

Myasthenia gravis is a chronic disease the characteristic feature of which is a variable degree of weakness following the use of various voluntary muscles, particularly those innervated by cranial nerves. The muscles of the neck, trunk and extremities are also commonly affected and respiratory insufficiency occurs in severe cases. Smooth and cardiac muscle are not involved. Physiologic studies have indicated that the basic defect is a failure of neuromuscular conduction which in certain respects resembles that due to curare. Until the development of methods of diagnosis and treatment made in the past two decades, myasthenia gravis was thought to be a rare disease. (Table I.) However, since 1930 there has been an increased recognition of cases making possible a more careful evaluation of the natural course of the illness. The most important contribution needed to our knowledge of this condition is the recognition of its etiology.

Perhaps the earliest clinical description of this disease was made by Willis in 1685.[1] In noting the different types of palsy he observed: "There is another kind of this disease depending on the scarcity of the spirits in which the motion fails wholly in no part or member, yet is performed but weakly only, or deprivedly by any. Those who being troubled with the scarcity of spirits, will force them as much as they may to local motions, are able at first rising in the morning to walk, move their arms this way and that, or to lift up a weight with strength; but before noon the stores of the spirits which influence the muscle being spent they are scarce able to move hand or foot. I have now a prudent and honest woman in cure who for many years had been obnoxious to this kind of bastard palsy, not only

TABLE I
YEAR DIAGNOSIS MADE IN PATIENTS WITH MYASTHENIA GRAVIS (JOHNS HOPKINS HOSPITAL)

Years	Measures Available for Diagnosis and Management	No. of Patients*
1905–09		0
1910–14		0
1915–19		0
1920–24		2
1925–29		6
1930–34	1930 ephedrine 1932 glycine 1934 neostigmine	22
1935–39		39
1940–44	1941 thymectomy	65
1945–49	1945 organic phosphate anticholinesterases	84
1950–53		52

* The number of new patients increased sharply with the introduction of measures helpful in diagnosis and management.

* From the Medical Clinic of the Johns Hopkins University and Hospital, Baltimore, Md.

in the limbs but likewise in the tongue. This person for some time speaks freely and readily enough but after long, hasty or laborious speaking, presently she becomes mute as a fish and cannot bring forth a word. Nay, and does

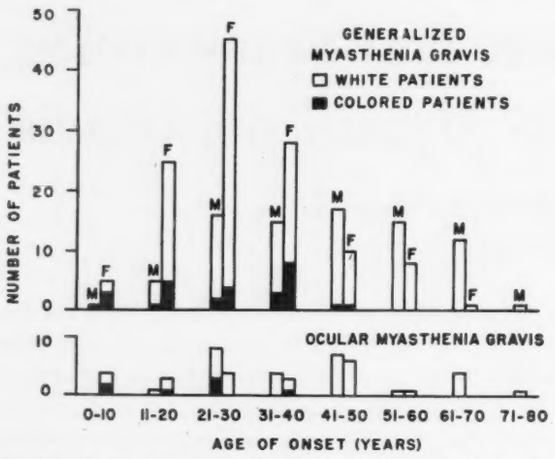

FIG. 1. Age of onset of disease in patients with generalized and with local ocular myasthenia gravis.

not recover the use of her voice until after many minutes."

This seminar may present a more detailed description of this disease than that of Willis. However, when the concluding paragraph is written, we will have described a state of knowledge little more advanced than when he wrote in conclusion: "The spirits residing in the brain are conscious of the weakness of the others placed in the members. They refuse to impose local motion on their companions as being a task too difficult for them, for which cause the affected are scarce led by any persuasion."

It is our purpose to present an analysis of 220 cases of generalized and 50 of localized ocular myasthenia gravis which have been observed over a period of many years. The latter group comprises those patients in whom clinical evidence of myasthenia has been restricted to the extraocular muscles and orbicularis oculi for at least two years. This group is considered separately even though special tests usually revealed changes in neuromuscular function in the extremities, and even though some of the patients will undoubtedly develop generalized symptoms at a later date. In addition to this analysis important observations concerning various aspects of this disease, its pathogenesis and treatment will be presented from the work of others.

Although the syndrome was described in the seventeenth century it was not until 1878 that the disease was recognized by Erb[2] as a form of bulbar paralysis which was singled out because of its tendency to spontaneous recovery. Jolly[3] in 1891 discovered the well known type of response of the muscles to electrical stimulation and first mentioned the possibility of physostigmine as a therapeutic agent. In 1901 Lacquer and Weigert[4] first described a thymic tumor in myasthenia gravis and suggested that it might be concerned in pathogenesis. Credit for placing the description of myasthenia gravis on a sound basis must go to Oppenheim[5] whose monograph was published in 1901. Harriet Edgeworth first noted the beneficial effect of ephedrine[6] and in 1934 Mary Walker[7] used eserine as a therapeutic agent. During those years intensive work was in progress concerning the chemical mediation of transmission at the neuromuscular and other synaptic junctions by the release of acetylcholine. These studies led to a re-examination of the basic defect in myasthenia gravis and the entire subject has remained an active one, as indicated in the previous seminars.

Clinical Picture. The outstanding feature of the weakness in this disease is its relationship to activity of the muscles. After a few repetitions of a given movement the power of contraction rapidly diminishes and may then quickly recover with rest. The muscle usually does not become painful or tender and the weakness in one group of muscles induced by repeated movement does not affect the function of others. In other words, the weakness cannot be correctly referred to as true fatigue.[8] In most cases certain of the muscles have a continually reduced function so that when the patient awakens there is residual weakness of varying degree and location. It is this basic weakness which does not disappear with rest that forms the most reliable description of the severity of the disease at any one period.

Myasthenia gravis knows no limitations with regard to geographic distribution and racial or sexual incidence. In our series the *incidence* of generalized myasthenia was higher in females (60 per cent being of this sex) while localized ocular myasthenia was more common in males (56 per cent). The *age of onset* (Fig. 1) of both types was lower in female than in male patients, the average being twenty-eight years in females and forty-two in males. The incidence of onset of generalized myasthenia reached a peak in the

third decade in females, while in males it was fairly uniform from the third through the seventh decade. Only one female patient developed myasthenia after the age of sixty, while in males weakness not uncommonly had its onset during the seventh decade and occasionally appeared during the eighth. Both generalized and ocular myasthenia began at an earlier age in colored patients in whom the disease did not develop after the age of fifty.

Multiple cases seldom occur in one family. However, one mother developed myasthenia several years after her daughter had died of the disease. Cases have been reported in siblings.[9]

The *initial episode* may appear precipitously, in which case the correct diagnosis may be overlooked and a vascular abnormality suspected. Involvement may be limited to a single muscle group and, as examples, paresis of one external rectus or of the extensor of one finger may be the only symptom for a considerable time. Since in half the cases of generalized myasthenia ptosis and diplopia were the first evidences of disease, it is important to emphasize the characteristic *ocular manifestations*. Ocular symptoms or signs are noted at some time in essentially all patients. Muscle weakness may occur unilaterally or bilaterally and in almost all combinations of functional disturbance. The variability from day to day in the ocular phenomena represents one of the most characteristic and diagnostic features. Weakness of the orbicularis oculi may occur, with or without ptosis. It is almost uniformly present when ptosis is evident and represents an important point in distinguishing the ptosis in myasthenia from that due to lesions of the oculomotor nerve. Weakness in closure of the lids is overlooked more often than any other common ocular sign. In none of our cases was a pupillary abnormality present. Retraction of the lid is a rare ocular sign which may be observed after long-standing ptosis. Visual fields and visual acuity are never altered as a direct result of myasthenia and difficulty in accommodation has been observed in only a few instances.[10] It is important to note the similarity of the ocular signs in myasthenia and in certain cases of hyperthyroidism. In localized ocular myasthenia the initial symptom was either ptosis or diplopia, except for two patients who complained of blurring of vision.

Once the disease has appeared the *course* may follow several patterns. There may be gradual extension of the involved areas leading to a relatively steady state of weakness which, once having reached its basic level, remains unchanged for many years, with the exception of moderate fluctuations in severity. In another group there is rapid progress both in the extent and severity of the involvement, sometimes terminating in death within a few months. In still others ocular manifestations may be the only evidence of myasthenia for many years. There is a tendency for the symptoms to fluctuate in severity from day to day and spontaneous remission sometimes lasting for many years may develop.

In our series 40 per cent of the patients with generalized myasthenia had developed widespread involvement within one month after onset. Thirty-four per cent had ocular manifestations alone for from one month to twenty-four years. In over half of these extension occurred from one to six months after the initial ocular symptoms, and in over three-fourths from one to twelve months. In 10 per cent extension occurred after two to five years of localized ocular myasthenia, and in the same number after six to twenty-four years.

The progressive developments which occurred as the course of the disease unfolded followed a rather characteristic pattern. In most instances the extraocular muscles were affected early, then the muscles of the face, including, first and most severely, the orbicularis oculi, then the frontalis and orbicularis oris (resulting in the characteristic myasthenic facies), the muscles of swallowing (resulting in nasal regurgitation and choking spells), of speech (resulting in a nasal voice), of mastication, the tongue, and the neck (especially the flexors, with soreness and difficulty in holding up the head). The upper extremities were usually affected before the lower and the proximal muscles before the distal muscles, so that among early complaints were difficulty in shaving and combing the hair. In the upper extremities the extensors were usually involved before and to a greater extent than the flexors, while in the lower extremities the reverse was often the case. The muscles of the trunk, abdomen and of respiration were among the last involved after the disease had become severe. About 10 per cent noted occasional numbness or tingling in the extremities or face.

During periods of improvement weakness of the extraocular muscles was frequently the last to disappear and the first to recur with an exacerbation. Although strength was usually

maximal on awakening and minimal at the end of the day, this was not invariable and some patients were just as weak on arising as at bedtime.

The average time interval from the onset of symptoms to the first episode of marked weakness experienced by the patient was eight months. The severity and rate of progression of symptoms were, in general, greater in male than in female patients. One five year old boy developed generalized myasthenia over a twenty-four-hour period but this rapid course was unusual.

TABLE II
NUMBER OF COMPLETE OR NEARLY COMPLETE REMISSIONS THAT OCCURRED IN 220 PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS

Time after onset of myasthenia gravis (yr.)	0–½	½–1	2–5	6–20	Total
Patients not receiving neostigmine	13	3	2	3	21
Patients receiving neostigmine	2	6	13	14	35
Duration of neostigmine administration (yr.)	(0.1)	(0.7)	(2.4)	(4.2)	(2.7)

Two to forty-six (average 9) years have elapsed since the onset of the disease in the patients with generalized myasthenia and all have received neostigmine at some time. Almost all have had numerous periods of exacerbation and other periods with variable degrees of improvement. Approximately one-fourth have had a real *remission* of their myasthenia during its course, as indicated by complete or nearly complete disappearance of weakness for at least six months. In some patients mild ocular symptoms persisted during the remission, and in others these recurred from time to time, particularly after emotional stress or upper respiratory infection. Others had mild "fatigability" which did not require medication. Most of the patients had only one remission while 9 per cent had two to four. The length of the remission varied up to seventeen years, with the average being 4.6 years. Almost half began during the first year but others occurred after many years (Table II), and the average time interval between onset of disease and of spontaneous improvement was four years. The administration of neostigmine did not appear to influence the incidence or duration of remissions. The duration was approximately the same in patients whose period of amelioration began early in the disease as in those whose remission began late. The incidence and duration of these episodes of relief appeared to be greater in female than in male patients, and in younger patients than in those in middle life.

Thirty-two per cent of the patients with generalized myasthenia died of the disease three months to twenty-five years after onset. Sixty-two per cent of the deaths occurred within three years and 85 per cent within six. The average interval between onset and death was 4.9 years. The mortality rate was higher in male patients and those in whom the disease began in later life.

The patients still alive have had the disease for an average of ten years. (Fig. 2.) Their course has been assessed by comparing their present status with that at the time of their first severe episode of generalized myasthenia or, if the myasthenia was not severe, at the time of occurrence of maximal symptoms. At the present time 12 per cent are in complete or nearly complete remission, 25 per cent have had moderate improvement in their basal strength and in their neostigmine requirement and response, 20 per cent are unchanged and 10 per cent have become worse. (Table III.)

The factors associated with *exacerbation* of the disease were most commonly upper respiratory infection, emotional tension and the postpartum period. In addition, most of the women complained of feeling weaker for several days to two weeks before the onset of each menstrual period. They were usually at their best strength during or shortly after the menstrual period.

Fifty patients studied had *myasthenia gravis localized to the extraocular muscles* during their entire period of observation. In contrast to the higher incidence of generalized myasthenia in females, ocular myasthenia was more common in males. These patients have been followed for two to forty-one (average 10) years without, as yet, clinical evidence of extension of the disease. Most noted several periods of improvement and exacerbation of symptoms and 62 per cent have had one or more complete remissions, for an average period of 1.5 years. At present 26 per cent are in remission, 52 per cent are unchanged and 18 per cent improved.

Most of these patients had weakness of the orbicularis oculi, and 12 per cent complained of "easy fatigability" or mild weakness of the arms and legs, but there was no change in strength of the peripheral muscles following

intramuscular neostigmine. The electromyogram was normal in eight patients studied, but the results of injection of neostigmine (1.5 mg.) into the brachial artery provided evidence of a mild degree of myasthenia in seven of eight patients.

The question invariably arises in patients with localized ocular myasthenia as to the likelihood of serious extension of the disease to other muscles. This problem is a frequent one as ocular manifestations were the presenting symptom in half of the patients with generalized myasthenia gravis. Of these patients 85 per cent developed extension within two years after onset and only 15 per cent after two years, half of these in two to five and half in six to twenty-four years. Therefore, a patient with localized ocular myasthenia of more than two years' duration has a good chance of not having extension of the disease.

Influence of Pregnancy and of Thyroid Disease. Many observers have noted that remission of myasthenia may occur during *pregnancy*.[11] There may be a relapse during the first trimester, but complete return of strength may accompany the final two trimesters and last for several months after term. However, examples in which the disease has grown worse or had its onset during pregnancy have also been reported.[12–14] In our patients information is available on the course of the disease during and after thirty-one preg-

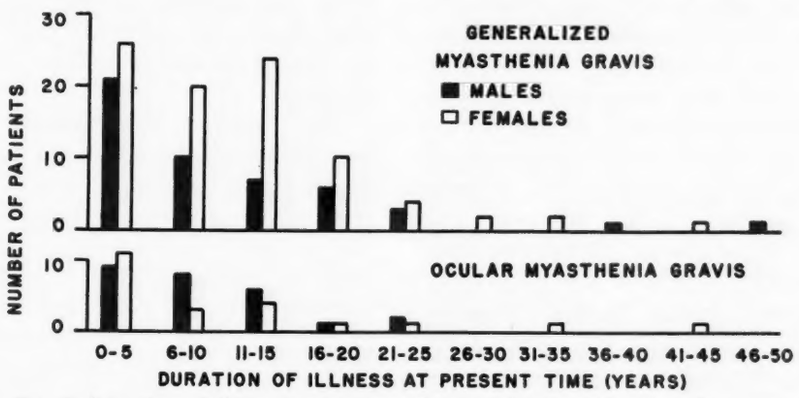

FIG. 2. Duration of illness in patients with generalized and local ocular myasthenia gravis.

TABLE III

COURSE OF GENERALIZED MYASTHENIA GRAVIS AND EFFECT OF THYMECTOMY AND OF IRRADIATION OF THE THYMUS

Sex	Procedure	No. of Patients	Duration of M. G. (yr., avg.)		Per cent				
			Living	Died	In Remission	Improved	Unchanged	Worse	Dead
M	None	46	9.3	4.0	15	11	7	17	50
	Thymectomy	19	10.0	3.6	21	21	16	0	42
	Irradiation	23	8.4	8.3	0	39	30	17	14
	Total	88	9.2	4.1	13	20	15	14	39
F	None	80	11.4	5.3	14	26	21	8	31
	Thymectomy	25	11.8	5.4	12	32	28	0	28
	Irradiation	27	8.6	6.7	4	33	26	20	20
	Total	132	10.9	5.5	11	29	24	8	28

nancies in twenty-four patients. The commonest association was moderate exacerbation of the disease after delivery which occurred in fourteen instances, including four in which remission had occurred during pregnancy. The exacerbation usually took place during the six weeks after delivery, being as early as eight days in one and as late as five months in another. Two patients became worse one week before delivery. In eight instances there was moderate to marked improvement during pregnancy, usually during the latter half, but in one patient improvement occurred in the second month. Five patients became worse during the first trimester and three had onset of the disease during the third trimester. Three improved after abortion (spontaneous or induced) during the first trimester, while two patients had onset of the disease three and eight weeks, respectively, after spontaneous abortion. During thirteen pregnancies there was no change in the disease and in ten no change after delivery.

Numerous authors have described a relationship between the onset or severity of myasthenia and disease of the *thyroid* gland. The disease may have its onset during elevated thyroid activity or appear after treatment when the patient is euthyroid.[15–17] Myasthenia has been reported both to have been improved and made worse by treatment of an existing hyperthyroidism or the administration of thyroid extract to a euthyroid individual.[18–20] Because generalized muscular weakness and impairment of extraocular movement are common in hyperthyroidism it is probable that some instances of association of the two diseases are overlooked. In the great majority of patients with hyperthyroidism and weakness the response to neostigmine is normal, excluding the presence of associated myasthenia gravis.

Of our patients twelve (5 per cent) showed some abnormality of the thyroid gland. Eight had hyperthyroidism. Treatment of the hyperthyroidism was usually followed by improvement in the myasthenia, and when hyperthyroidism recurred in one case there was an exacerbation of the weakness. In addition, myasthenia gravis developed in three euthyroid patients during dessicated thyroid administration for weight reduction and, in another euthyroid patient who had ocular myasthenia gravis and exophthalmos (post-thyroidectomy), administration of this drug, in an effort to reduce the exophthalmos, was followed by fulminating myasthenia gravis. On the other hand six euthyroid myasthenic patients received dessicated thyroid without effect on their strength. A diverse relationship occurred in three patients in whom myasthenia gravis appeared one month, three and seven years after subtotal thyroidectomy. Six myasthenic patients, of whom five were male, had exophthalmos in the absence of thyroid disease or of any history of thyroid disease.

The Thymus. Abnormalities of the thymus are frequently found in patients with myasthenia gravis. In approximately one-third of the reported cases a thymic tumor has been present and in other instances hyperplasia was noted, with the presence of germinal centers in the medulla.[21] It has been thought that, in view of the similarity of myasthenia gravis to the effects of curare administration, there might be a curariform substance formed in the abnormal thymus gland. In numerous cases a thymectomy has been performed, and several investigators have studied extracts of these thymuses and glands from normal animals in regard to their action on neuromuscular function.[22–27] The results of these studies have been so variable that no conclusions can be drawn.

Of sixty patients in our series who either had a thymectomy or came to autopsy 53 per cent had a hyperplastic thymus with germinal center formation, 23 per cent a thymoma, which in one instance had metastasized to the pleura, 8 per cent a persistently enlarged thymus which was normal microscopically, and the remainder either a normal appearing thymus or no detectable thymic tissue. In spite of the greater number of female patients in this series (34 to 26) thymomas were more common in males (8 to 6). In general, the patients who had a thymoma developed a more severe form of the disease with a higher mortality rate. Of those patients still alive and in whom the status of the thymus was known as a result of operation, 10 per cent had a thymoma, while of those patients who died 38 per cent had a tumor. However, not all patients in whom there is a tumor in association with myasthenia have a poor prognosis. Of three in whom a thymoma was removed and who are still alive, one has had a complete remission lasting ten years, one has improved and the other has shown no change. There were, in addition, three patients who had a mediastinal mass detectable by x-ray who have not had a thymectomy. Two have had a benign myas-

thenia over many years. The other patient has had a fulminating type of weakness which has been steadily progressive.

Methods Used in Diagnosis. The muscular weakness in myasthenia responds dramatically to the administration of neostigmine which has formed the basis for a diagnostic test.[28,29] Atropine is always given along with 1.5 or 2 mg. of neostigmine in order to prevent the stimulating effect of the latter drug on the smooth muscle of the intestines, and other unpleasant effects which may result. Improvement in strength begins in the involved muscles within five minutes after intramuscular injection, and the maximum effect may be expected within thirty minutes. In regard to the ocular muscles it is essential to remember that the levator responds more readily than do the muscles attached to the eyeballs, as failure to appreciate this fact may result in misdiagnosis. In children the extraocular muscles may be particularly resistant to the effect of neostigmine. In order to interpret the effect of this drug properly on the strength of the ocular muscles it is wise to have a systematic method of recording the observations. The width of the palpebral fissures should be noted both with the eyes held wide open and with them open and at rest. Using a perimeter the movement of each eye is recorded in the four directions. The normal range is up 40 degrees, down 60 degrees, out 45 degrees and in 45 degrees. These readings are repeated thirty minutes after injection of the neostigmine. In those patients whose major difficulty is dysphagia the use of the fluoroscope with barium swallow before and after neostigmine has been utilized by Viets[30] as a diagnostic maneuver. There is no question of voluntary control in these movements and retention of barium in the pyriform sinuses after neostigmine is evidence of a structural disease affecting the swallowing mechanism. Care must be taken that the patient does not aspirate barium and a thin mixture should be used. The intravenous administration of neostigmine[30a] or of a related compound, edrophonium (tensilon),[30b] has been employed as an aid in diagnosis, but has little advantage over intramuscular neostigmine other than rapidity of action. Edrophonium is of interest in that it has only mild anticholinesterase action and appears to affect neuromuscular function directly.

In mild cases the objective changes may be so meager that one cannot observe sufficient clinical improvement following neostigmine to make a certain diagnosis. Under these circumstances one may administer a very small dose of curare[31] or quinine[32] to bring about an aggravation of symptoms, following which the muscle function may be restored by neostigmine. Such tests should be done with care as a critical exacerbation of the symptoms, with respiratory dysfunction, may result.

In seven patients with severe generalized myasthenia there was little improvement in strength following 1.5 mg. of neostigmine, even when this was administered early in the disease. Three of these patients had an increasing response to 1.5, 2, 3, 4 and 5 mg. of neostigmine. Thus one, whose grip strength was 1 kg. (spring dynamometer) in the basal state, had a grip of 3, 7, 12, 20 and 25 kg. after these doses. Following 2 mg. of neostigmine administered by artery, the strength of the arm increased to 35 kg., indicating that the doses injected intramuscularly were insufficient to attain maximal response.

Neostigmine has been given to many normal subjects and patients with weakness due to other causes. In no instance has the strength of any muscle group other than the extraocular improved to a greater extent than followed a placebo. Definite improvement developed in four patients with ptosis and limitation of extraocular movement which proved to be due to multiple sclerosis in two instances, to arteriosclerotic cerebral vascular disease in one and to widespread muscle necrosis of unknown etiology in the other. The occurrence of abundant fasciculations in weak muscles following neostigmine may be of aid in excluding myasthenia since muscles seriously affected by this disease rarely fasciculate.

Treatment. It is important to make the patient familiar with the nature of his disease and the objects of treatment. Neostigmine does not produce a "cure." In the average case with proper management the prognosis for a relatively normal life is good. No two patients will have the same response to treatment and in each case variations must be made from time to time to take care of fluctuations in the intensity of the disease. The primary object of treatment is to provide the greatest increase in strength possible and to maintain this increase at a sustained level throughout the day. The patient must be taught to regulate his own dosage of neostigmine. It may be of help, particularly in the initiation

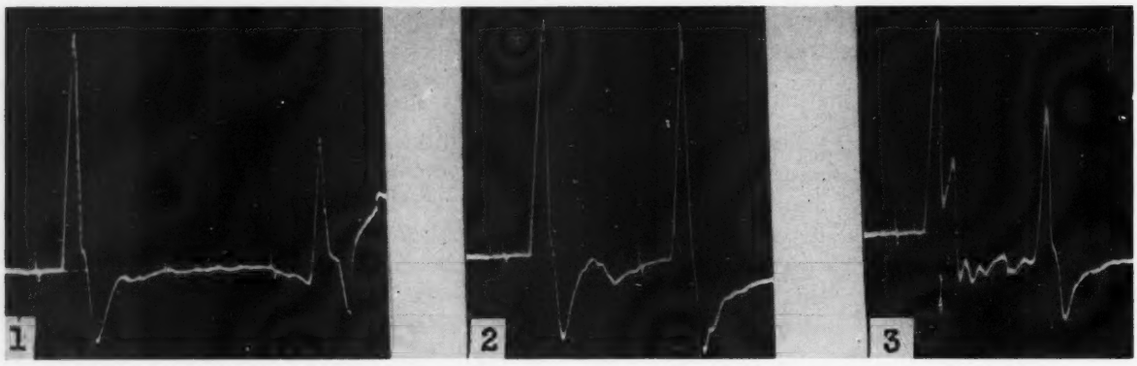

FIG. 3. Electromyogram of a patient with myasthenia gravis showing: (1) Depression of the second muscle action potential in response to a pair of supramaximal nerve stimuli when the patient had received no medication for seven hours. (2) Repair of block in neuromuscular conduction after 0.5 mg. DFP intra-arterially. (3) Block in neuromuscular transmission with development of repetitive discharge following 0.5 mg. neostigmine (twenty-nine minutes after record 2). This type of block is different from that due to myasthenia gravis, and is similar to that seen in the normal individual after a smaller dose of anticholinesterase agent. (After HARVEY, LILIENTHAL, GROB, JONES and TALBOT. *Bull. Johns Hopkins Hosp.*, 81: 267, 1947.)

of the treatment program, to give the patient a mimeographed outline with headings for the date, time of day, meals and medications and a space for tallying his own estimate of strength.

Almost all of our patients with generalized myasthenia have been managed with neostigmine. First, the maximum effect on muscle strength was determined by the response to an intramuscular injection of 1.5 to 2 mg. Then, the drug was administered orally until this maximal effect was achieved. Most patients could be satisfactorily regulated by 15 to 45 mg. of neostigmine bromide orally at two- to four-hour intervals. Only severely ill patients required neostigmine during their sleeping hours. When swallowing was impaired the schedule was adjusted so that meals were served about forty-five minutes after a dose of neostigmine and, if necessary, this dose was larger than others. Patients unable to swallow tablets were given neostigmine intramuscularly, usually in doses of 1 to 2 mg. every one to three hours.

The majority of patients have continued to respond well to this drug over a period of years. Increased amounts were necessary during periods of exacerbation, and the demand sometimes changed rapidly during even a minor infection. In patients with severe progressive myasthenia, the response to neostigmine gradually diminished, and increasing doses of the drug were given, (as much as 1,200 mg. (80 tablets) a day by mouth or 48 mg. intramuscularly) with but little effect on strength.

Careful administration of tetraethylpyrophosphate (TEPP)[33] or octamethyl pyrophosphoramide (OMPA)[34] resulted in most patients in better sustained strength and endurance than was possible with neostigmine. These drugs produce partly irreversible inhibition of cholinesterase enzymes. TEPP and OMPA were given by mouth two or three times a day and the increase in strength was fairly evenly maintained throughout the day and night. The average daily maintenance dose was 16 mg. In patients with severe myasthenia these drugs were supplemented by 15 to 30 mg. of neostigmine administered orally two or three times a day, preferably an hour after a dose of TEPP or OMPA. The maximum strength attained with any of these drugs, or with their combination, was approximately the same. Patients whose strength responded poorly to large doses of neostigmine were helped but little by TEPP or OMPA. It is difficult to administer too much neostigmine to a patient with severe myasthenia, but an overdose of TEPP or OMPA, or the administration of neostigmine to a patient who has received too much of these drugs (Fig. 3), may result in generalized fasciculations and profound weakness, including the muscles of respiration.[33]

The action of TEPP and OMPA differs from that of neostigmine in that single doses of the latter drug exert graded effects on muscle strength which vary with the size of the dose, whereas TEPP and OMPA exert no effect on strength until a large total dose has been administered, following which the effect can be increased or maintained by smaller doses. In the case of TEPP the initial "priming" dose

(40 mg.) can be given over a twenty-four-hour period and regulation rapidly achieved. OMPA has a latent period of several hours before the action of any given dose is manifest. This is reflected by a longer interval between administration and depression of cholinesterase activity of the plasma and red blood cells, and is apparently due to the time required for conversion of OMPA, which does not itself have anticholinesterase activity, to an anticholinesterase compound of unknown constitution, presumably by the liver.[35] Thus initial regulation on OMPA requires several days. OMPA has less marked central neural effects than TEPP and has greater stability in propylene glycol solutions.

Patients with myasthenia have, in general, a higher threshhold for the development of the parasympathomimetic effects of anticholinesterase compounds than do non-myasthenic subjects. However, most patients develop excessive salivation and gastrointestinal symptoms, and it is surprising how often the source of these symptoms is not appreciated. Most patients under treatment with neostigmine received 0.6 mg. of atropine one to four times a day to prevent these side effects. The latter drug is longer acting, and patients taking 1 or 2 mg. of neostigmine intramuscularly every two hours required 0.3 mg. of atropine only every four hours.

About a third of the patients given ephedrine as an adjuvant to neostigmine experienced a slight additional increase in strength. ACTH and cortisone are reported to have favorably influenced the course of myasthenia gravis,[36,37] but administration of these hormones to sixteen patients revealed no change in eight, increased weakness in seven and improvement in only one.[38]

The administration of curare, quinine, quinidine, morphine and, in some instances barbiturates, may be hazardous. Curare is the most dangerous drug since myasthenic patients are very sensitive to its effects. Of the other muscle relaxing agents, flaxedil[39] is also dangerous while decamethonium and succinylcholine are better tolerated.[39,40] However, it is best not to administer any muscle-relaxing agents to myasthenic patients. Since morphine may depress respiration and since its effects may be potentiated by anticholinesterase compounds, it must be used with caution. Two myasthenic patients died within a few hours after the injection of 8 and 16 mg. of morphine sulfate. Demerol is usually well tolerated although it is best to begin with half the usual dose. Mild sedatives may be used in most cases, but those who are having difficulty swallowing or breathing may develop serious difficulty.

Procaine and its derivatives have neuromuscular blocking action[41] and should be administered with caution. However, a number of severely ill patients had dental extraction following local procaine infiltration, without untoward effect, and one had a herniorrhaphy performed under local xylocaine anesthesia. Ether was well tolerated by myasthenic patients, as was cyclopropane.

Antibiotics, chemotherapeutic agents, and suction were of help in avoiding and combatting pulmonary infection in patients who had weakness of cough, respiration and swallowing, and particularly in patients who were confined to the respirator.

Impairment of breathing, with lack of response to large doses of neostigmine, necessitated artificial respiration and oxygen. Since patients who had difficulty breathing almost always had difficulty swallowing, it was found desirable to perform a tracheotomy before the patient was put in the respirator. While the mortality of patients who required prolonged artificial respiration was high, four patients who had been confined to a respirator for more than six months improved to the point of being able to leave the respirator for over half a year and one of these has performed full time household duties for the past two years.

Thymectomy. In 1941 it was believed that in order to evaluate the possible relationship of the thymus to the pathogenesis of myasthenia total extirpation of all thymic tissue should be undertaken in a series of cases.[42] Since that time forty-four patients, nineteen male and twenty-five female, have had a thymectomy in this hospital and have been observed for two to twelve years (average six years). The average severity in these cases was greater than in other patients in this series. The average duration of the disease at the time of surgery was three years but one-third of the patients were operated upon during the first year of their illness. In general, the course of the disease in these patients has been only slightly better than in those who had neither thymectomy nor irradiation of the thymus. (Table III.) Approximately the same proportion have died in each group and the number who have had striking remissions is

similar. Perhaps a slightly greater number have improved and fewer patients have become worse since thymectomy, but the differences between this group and those not operated upon is disappointingly small. The course of female patients following thymectomy has been slightly better than in the males, but this is also true of patients who were not operated upon. Younger patients have also done better than older patients following the operation, but again, so have younger patients not subjected to thymectomy.

Forty patients have had irradiation of their thymic region with a total of 2,000 r administered anteriorly in divided doses over a period of ten days. Again the difference between this group and those not receiving such treatment has not been significant. Some of the results following both types of treatment have been dramatic, with return to normal strength within several weeks and no relapse through periods up to twelve years. However, in a disease in which there is such a pronounced tendency toward spontaneous variability it is extremely difficult to know whether favorable results stem from the therapeutic procedure or represent an unrelated change.

Thymectomy has now been carried out over a number of years in several large clinics. Keynes[43] has summarized his results in 155 cases. He divides the patients into four categories: (1) quite well with no symptoms and no neostigmine, (2) virtually well with minimal symptoms, small dose of neostigmine, (3) improvement often considerable, neostigmine still necessary, and (4) no change. After deducting those cases in which a thymoma was found and those who died postoperatively, there remained 120 cases which on analysis were placed in the four categories outlined above as follows: (1) 32.5 per cent, (2) 33.3 per cent, (3) 25.8 per cent and (4) 8.3 per cent.

Viets[44] has stated that he selected patients for operation who had had the disease for a considerable period and in whom the effects of neostigmine were known, so that there would be a suitable basis for evaluation. All but four of twenty-nine patients without a thymoma have survived and the results are classified as: excellent in three, good to excellent in two, good in five, fair to good in two, fair in two, poor to fair in two, poor in two, and too early to estimate in the remaining seven. It is his impression that the results to date justify continuation of the operation.

Eaton and Clagett[45] reviewed their observations involving over 300 patients seen since 1941. Of this series sixty-two cases had the thymus removed and were compared to a selected group of fifty-six patients not undergoing surgery. Their conclusions were that the chance of a remission following surgery was 35.5 per cent as contrasted to a 28.5 per cent chance that a similar remission would develop without operation. It is their belief that thymectomy does not exert a beneficial effect.

It may be concluded that there is not yet sufficient information available for final evaluation of the role of thymectomy in the treatment of myasthenia gravis. In our opinion this operation, if performed at all, should be reserved for those patients in whom there has not been a satisfactory response to drug therapy and those severe cases in which the course of the disease followed over a period of time suggests that the chance for a spontaneous remission is small. It should probably also be performed in patients who have x-ray evidence of a thymoma, because of the possibility of local extension or, rarely, of pleural metastases.

Etiology and Pathogenesis. The general nature of this disease suggests that it is an endocrine or metabolic disorder. As pointed out, the occurrence of thymic abnormalities is so frequent that it seems difficult to discard the possibility that this gland may elaborate some substance responsible for the myasthenic symptoms. Attempts to isolate a humoral material have been carried out, but there has been no confirmation of the claim of Torda and Wolff[46] that there is a factor in the serum of these patients which inhibits the synthesis of acetylcholine. The close relationship of the course of the illness in certain instances to disease of the thyroid has been commented upon, and Torda and Wolff[47] have described an excess of an acidophilic substance in the anterior lobe of the pituitary. Beneficial effects following the administration of ACTH and cortisone have been reported by various authors, but in our experience these substances have not been helpful. Of interest in regard to the possibility of some circulating agent producing the defect in neuromuscular transmission are the cases reported in which newborn infants of myasthenic mothers have exhibited weakness which was alleviated by neostigmine and which persisted for only the first few weeks of life. Twenty such cases have been reported in the literature.[48–53] One patient in our series had

a newborn infant who became weak shortly after birth and whose weakness responded to neostigmine. This infant recovered completely in three weeks and has remained well. It has been postulated that the weakness is due to a circulating substance which passed through the placenta from the maternal circulation. Observations have shown that D-tubocurarine and decamethonium do not cross the normal placental barrier.[54,55]

TABLE IV

THRESHHOLD CONCENTRATIONS OF INTRA-ARTERIAL ACETYLCHOLINE THAT PRODUCED STIMULATION AND DEPRESSION

	No. of Subjects	Lowest Dose (mg.) of Intra-arterial Acetylcholine That Produced Flexion Twitch			No. of Subjects	Lowest Dose (mg.) of Intra-arterial Acetylcholine That Produced Depression of Action Potentials		
		(Range)	(Avg.)	(S.D.)		10% (Avg.)	50% (Avg.)	100% (Avg.)
Normal	17	0.2–5.0	1.5	1.8	5	1.7	3.7	9.0
Ocular myasthenia gravis	7	0.2–4.0	1.1	1.2	1	2.0	5.0	10.0
Generalized myasthenia gravis	17	0.2–10.0	2.8	2.5	6	1.4	3.4	7.3

When the nerve to an involved muscle in this disease is stimulated electrically by a rhythmical series of impulses, the muscle response fails progressively. Hoffman[56] was the first to demonstrate that the greater the frequency of stimulation the more marked the myasthenic reaction. He noted that exhaustion of muscle occurred following stimulation with faradic current at the rate of seventy-five interruptions of current a minute, whereas stimulation immediately afterward at the rate of seventeen interruptions a minute gave rise to contractions. More detailed electromyographic studies by Lindsley[57] and, using a more reproducible and quantitative technic by Harvey and Masland,[58] have shown that the defect in neuromuscular transmission has similarities to that produced by curare.[59] These phenomena are restored toward normal by the administration of neostigmine.

Various observations suggest that this defect in transmission is due to an alteration in the acetylcholine mechanism. This could result from: (1) an excessive concentration of cholinesterase at the neuromuscular junction; (2) from elevation of the excitatory threshhold of the muscle end plate to the normal amount of acetylcholine released by each nerve impulse; or (3) from failure of each nerve impulse to release a normal quantum of acetylcholine. The first possibility seems unlikely in view of the repeated finding of normal cholinesterase activity in homogenates of affected muscle,[60,61] although studies on the precise concentration of this enzyme at the neuromuscular junction in myasthenic patients have not been carried out. Studies were carried out to test the validity of the second possibility by the intra-arterial injection of acetylcholine in normal and myasthenic subjects, comparing the threshhold concentration necessary to evoke an involuntary flexion twitch of the injected fingers and hand. Preliminary observations had suggested that myasthenic patients might be more reactive to injected acetylcholine than normal subjects,[62,63] but later studies revealed wide variation in threshhold to acetylcholine in different subjects and even in the same subjects.[64–67] There is a tendency for the stimulation threshhold to be higher in myasthenic subjects.

Recently[68] an attempt has been made to compare not only the threshhold to the stimulating effect of acetylcholine, but also the depressant effects of higher concentrations. Graded doses of acetylcholine were injected into the brachial artery, and recordings were made of the muscle action potentials elicited by trains of 4 supramaximal stimuli applied to the ulnar nerve at two-second intervals before and after injection. The amount of acetylcholine that produced uniform depression of the muscle action potentials

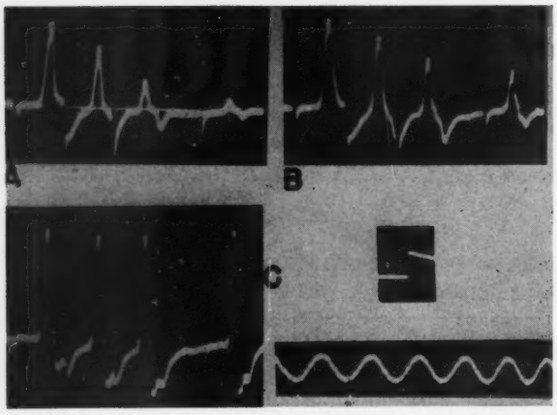

FIG. 4. Progressive depression of muscle action potentials in response to repeated supramaximal stimulation of the ulnar nerve at 16 msec. intervals in a patient with myasthenia gravis before neostigmine (A), and partial recovery ten minutes after injection of 2 mg. neostigmine into the brachial artery (B). The response of a normal subject to the same train of stimuli is shown in (C). Calibration = 16.6 msec. (After HARVEY, LILIENTHAL and TALBOT. *Bull. Johns Hopkins Hosp.*, 69: 547, 1941.)

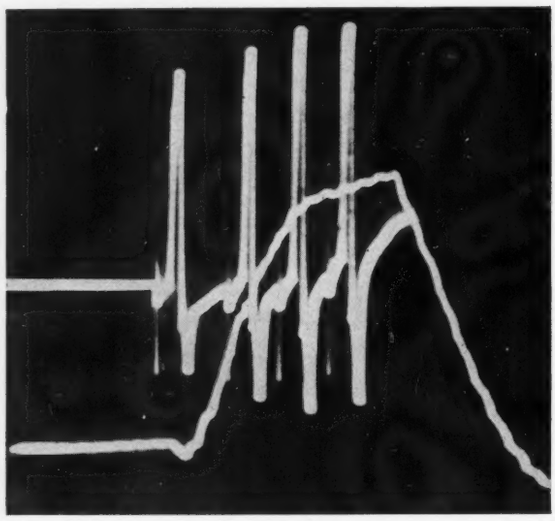

FIG. 5. Facilitation (increase) of consecutive muscle action potentials of a patient with myasthenia gravis in response to a train of supramaximal nerve stimuli separated by 16 msec. intervals. Mechanical response of the muscle (isometric) is recorded below.

was not significantly different in normal subjects and in those with myasthenia gravis. (Table IV.)

By taking serial recordings of the muscle action potentials before and after the injection of acetylcholine it was observed that concentrations in the range of the stimulating threshhold dose corrected for a period of several seconds both the depression (Fig. 4), and when present, the facilitation (Fig. 5) seen in patients with generalized myasthenia. The injected acetylcholine transiently increased the size of the muscle action potentials so that they all equalled that of the largest potential in the control records. This observation confirms the existing belief that acetylcholine is capable of correcting the defect in neuromuscular transmission in myasthenia gravis.

When 0.3 to 1.2 mg. of neostigmine was injected intraarterially, the threshhold to both the stimulating and depressing effects of acetylcholine was lowered by fifty to one hundredfold.[68] The degree of lowering of the threshhold was apparently equal in myasthenic and nonmyasthenic subjects. This suggests that the rate of destruction of the injected acetylcholine was essentially the same in both groups.

A number of investigations have been carried out in the search for a substance in the tissues and body fluids that might be responsible for the impairment of neuromuscular function, or for a substance capable of inhibiting the synthesis of acetylcholine.[69–72] However, a number of different experimental technics have been used and the results reported have been so variable that no conclusions can be drawn about this phase of the subject at this time.

TOXINS AND DRUGS AFFECTING NEUROMUSCULAR FUNCTION

Botulinus toxin may produce weakness or paralysis of both voluntary and smooth muscle. The eye muscles are affected early, resulting in blurring of near vision due to paralysis of accommodation, dilated and fixed pupils, diplopia and ptosis. The bulbar muscles may be affected next, and finally the skeletal and respiratory muscles. The manifestations may resemble those of myasthenia gravis, but the rate of appearance and of progression of symptoms is slower in the latter disease. In addition, the weakness of botulism is unaffected by neostigmine. In former years severely ill patients died; but if kept alive by the use of antibiotics, tracheotomy and artificial respiration function may begin to return in seven to fourteen days and recovery may be complete.

The effects of botulinus toxin are due to block of transmission at the neuromuscular junction and at parasympathetic nerve endings. The neuromuscular block differs from that due to myasthenia gravis in that motor nerve tetani

are well maintained, the summation curve for two stimuli is normal, and the paralysis is unaffected by anticholinesterase agents, potassium or epinephrine.[73–75] In contrast to curare, which acts by blocking the action of acetylcholine at the end plate without decreasing its release from the motor nerve endings, botulinus prevents its release without affecting reactivity of the end plate to this substance. It is not known whether the toxin interferes with the synthesis of acetylcholine or with its release from the terminal fibers of the motor nerve. One group of investigators has reported that the toxin strongly inhibits the enzyme which acetylates choline,[76] but another group was unable to confirm this.[74] Diminution in the response to direct stimulation of muscle has been reported[77] which, if confirmed, suggests that the toxin may also have a direct effect on muscle. Botulinus antitoxin is effective only if given in large doses before paralysis develops. In guinea pigs poisoned with one lethal dose of crystalline toxin (3×10^{-5} micrograms), paralysis became complete in slightly more than forty-eight hours.

Organic Phosphate Anticholinesterase Compounds. Several esters of phosphoric acid are potent inhibitors of the cholinesterase enzymes and have been used for a variety of purposes. Diisopropyl fluorophosphate (DFP) has been employed to study the role of cholinesterase enzymes in normal function and in disease[78] and as a therapeutic agent in a number of situations in which a cholinergic effect is desired, such as paralytic ileus, urinary retention and glaucoma.[79] TEPP and OMPA have been of value in the management of some patients with myasthenia gravis.[33,34] The usefulness of these compounds in therapy has been limited by the relatively narrow margin between the doses which are effective therapeutically and the doses which are toxic. The potent effects of the organic phosphate anticholinesterase compounds in animals of all species have led to their widespread use as insecticides (parathion, TEPP, hexaethyl tetraphosphate (HETP), and mipafox). The handling and dispersal of these compounds has resulted in a number of fatal exposures.[80,81] Finally, a group of related compounds, the "nerve gases," are, because of their volatility and toxicity, among the most potent of the known chemical warfare agents.[82]

The mechanism of action, effects, prevention and treatment of symptoms produced by members of this group of compounds are in general similar. The effects produced are attributable to accumulation of acetylcholine in smooth and cardiac muscle and secretory glands (muscarine-like effect), motor nerves to striated muscle and preganglionic nerves to autonomic ganglia (nicotine-like effect) and the central nervous system. If exposure to these compounds does not prove fatal, complete recovery almost always ensues. However, persistent paralysis of the extremities with loss of tendon reflexes and muscle atrophy has been reported in three cases,[83,84] one following exposure to parathion and two to mipafox. Electromyographic studies showed no evidence of neuromuscular block and were similar to those seen in peripheral neuritis. These cases resemble those produced by tri-ortho-cresyl phosphate ("ginger jake paralysis"). Demyelination has been observed in the peripheral nerves and spinal cords of experimental animals following the administration of mipafox and tri-ortho-cresyl phosphate.[85,86]

The treatment of symptoms produced by anticholinesterase compounds relies primarily on atropine, which has a moderate inhibitory effect upon the muscarine-like manifestations, a mild to moderate effect on the central neural involvement and no influence on the nicotine-like effects. In case of moderate or severe exposure large doses must be administered, and a mild degree of atropinization maintained for at least forty-eight hours. Patients who have symptoms due to systemic absorption of these agents have increased tolerance for atropine, so that large doses must be administered before signs of atropinization appear. Respiratory depression requires prompt artificial respiration. If convulsions are prolonged, interfere with respiration and are not relieved by intravenous atropine, the careful administration of trimethadione (tridione) may be of value.

This seminar has been presented with the hope that others will be stimulated to study the many problems in this field. As Osler stated in 1885:[87] "It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusion the accumulated facts seem to point; and to ascertain in what direction we may look for fruitful investigations in the future." The growth of interest in disorders of neuromuscular function, which is illustrated by this series of seminars, and the development of quantitative methods

for their study in man, lend encouragement to the hope that these investigations will be "fruitful."

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Clinico-pathologic Conference

Fever, Pharyngeal Ulcer, Pulmonary Infiltration and Hepatosplenomegaly

STENOGRAPHIC REPORTS, edited by Robert J. Glaser, M.D. and David E. Smith, M.D. of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, G. C. (No. 217068), was a white married housewife, fifty-three years of age, who was admitted to the Barnes Hospital for the first time on December 9, 1952, because of vomiting and abdominal pain. The family history was non-contributory. The past history revealed that the patient had had hypertension for at least fifteen years. Although she had been relatively asymptomatic in this regard except for occasional epistaxes, one year prior to admission she had an episode of severe crushing substernal pain which was relieved by analgesics and did not recur. She was kept in bed for only a few days. Three months before hospitalization she noted the onset of progressive exertional dyspnea and orthopnea, and three weeks before admission she was digitalized for these symptoms without improvement. Mild dependent bilateral ankle edema had been present for many years and had been unchanged in recent months. Ten years prior to entry the patient had had a bilateral oophorectomy and a hysterectomy for "tumor." The nature of the tumor was not known. One year before admission she fell and fractured her left humerus and six ribs. She recovered uneventfully.

For an indeterminate number of years the patient had suffered from occasional episodes of burning epigastric pain which most often followed the ingestion of "acid foods"; the pain, which had never awakened her from sleep, was not relieved by other foods or antacids. For several years she had noted mid-epigastric tenderness. Two months before admission the epigastric pain had increased in severity and subsequently was present constantly, radiating through the abdomen to the back, and being accentuated by ingestion of any kind of food. During the same period she had pain in her upper back which apparently was precipitated by motion and which radiated around the thoracic cage into the anterior chest. She was unable to define the nature of the pain. Three weeks prior to hospitalization she swallowed an orange seed which she believed had remained lodged in her throat. Since that time she had had constant dull pain in the right side of the throat, associated with some dysphagia. Subsequently she had vomited all solid foods and soft liquids within an hour after their ingestion, and had lost twenty-three pounds prior to admission. She denied melena and hematemesis.

At the time of admission physical examination revealed the patient's temperature to be 37°C., pulse 90, respirations 32, blood pressure 130/100. The patient was a well developed, thin white woman who appeared chronically ill. She complained of epigastric pain. She was mildly dyspneic and tachypneic but alert and cooperative. There was distinct evidence of weight loss. Examination of the eyes revealed the pupils to be round, regular and equal and to react to light and accommodation. The fundi showed narrowing of the arterioles with A-V nicking but no hemorrhages or exudates. The optic discs appeared normal. Examination of the upper respiratory tract was of interest because of the presence of a shallow ulcer, 0.5–1.0 cm. in diameter, at the apex of the right tonsillar fossa. The base of the ulcer was grey and the edges ragged. The cervical veins were not distended. There was no significant lymph node enlargement. Examination of the chest revealed it to be resonant to percussion. Breath sounds were decreased over both bases posteriorly. The left posterior ribs and upper dorsal vertebrae were tender to palpation. Cardiac borders were not readily discernible by percussion and no definite enlargement was detected. The sounds were distant, the rhythm regular and there were no

significant murmurs. The breasts were normal. The abdomen was minimally distended and there was marked tenderness in the right upper quadrant of the epigastrium. The liver edge was palpable to 2 to 4 cm. below the right costal margin and was firm and tender. The spleen tip was not tender but could be palpated at the left costal margin. There was mild cyanosis of the nail beds and minimal ankle edema. Neurologic examination was negative.

The laboratory data were as follows: red blood cell count, 4,730,000; hemoglobin, 15.0 gm. per cent; white blood cell count, 5,400; differential count: 1 per cent basophils, 2 per cent eosinophils, 17 per cent stab forms, 62 per cent neutrophils, 11 per cent lymphocytes and 7 per cent monocytes. Urinalysis: specific gravity, 1.010; albumin, negative; sugar, negative; sediment, occasional red blood cell and white blood cell and many bacteria. Stool: guaiac negative. Cardiolipin test: negative. Corrected sedimentation rate (Wintrobe): 9 mm. per hour. Blood chemistry: sodium, 135 mEq./L.; potassium, 5.3 mEq./L.; chloride, 93 mEq./L.; carbon dioxide combining power, 25 mEq./L.; total protein, 5.4 gm. per cent; albumin, 3.7 gm. per cent; globulin, 1.7 gm. per cent; sodium bilirubinate, 0; bilirubinglobin, 0.44 mg. per cent; bromsulphalein retention, 29 per cent in thirty minutes; cephalin-cholesterol flocculation test, 3 plus; thymol turbidity test, 7.6 units; alkaline phosphatate, 8.0 Bodansky units; prothrombin time, 52 per cent of normal; uric acid, 3.1 mg. per cent. Roentgenogram of the chest: hilar calcification, cardiac enlargement, questionable lymphangitic (metastatic) carcinomatosis. Metastatic series: hypertrophic arthritis of the lumbar spine; marked calcification of the abdominal aorta and iliac vessels; compression of second lumbar vertebra (question of fracture); splenomegaly. Electrocardiogram: borderline record with inverted T waves in leads 3 and AVF.

After admission the patient continued to complain of dysphagia and ate poorly. Abdominal pain was well controlled with mild analgesics and anti-spasmodic agents. On the first hospital day her temperature rose to 38°C. and she was given an injection of penicillin. Subsequently her temperature was found to be normal and the antibiotic was discontinued. On the fourth hospital day fine inspiratory rales were heard over the posterior lung bases. Circulation time with decholin was thirteen seconds. The following day the patient became febrile and on the sixth hospital day she had a shaking chill followed by sharp temperature elevation to 40°C. Physical signs compatible with consolidation in the lower lobe of the left lung were noted. A blood culture drawn at this time was sterile, and the white blood cell count was 5,750, with a differential count showing 3 per cent eosinophils, 12 per cent stab forms, 61 per cent neutrophils, 21 per cent lymphocytes and 3 per cent monocytes. Penicillin therapy was reinstituted and streptomycin was also administered. The patient's temperature remained elevated, however, averaging about 38°C.

A gastrointestinal x-ray series was performed and revealed hepatosplenomegaly with external pressure on the fundus of the stomach. An anteromedial bulge of the right diaphragm was also detected. The barium enema was negative. Repeated examinations of the stool for occult blood were negative. The patient was seen in consultation by an otolaryngologist who considered the pharyngeal lesion consistent with either a severe systemic disease or malignancy. During the first few hospital days the ulcer healed partially, and according to the consultant, its appearance no longer suggested malignancy.

On the eleventh hospital day the patient's temperature was still elevated, and dullness to percussion, diminished breath sounds and numerous post-tussic rales were heard over the left posterior lung base. The decholin circulation time was again determined and found to be seventeen seconds. Because it was thought that the fever might be due to drug hypersensitiveness, penicillin and streptomycin were discontinued on the twelfth hospital day. The febrile course, however, continued unabated. A biopsy of the pharyngeal ulcer was performed at this time. On the sixteenth hospital day the patient was noted to have dullness, decreased breath sounds and numerous medium inspiratory rales at both lung bases. Another roentgenogram of the chest was obtained and revealed cardiac enlargement of the left ventricular type, pulmonary congestion, compression fracture of the seventh dorsal vertebra, old fractures of the seventh, eighth and ninth ribs and of the left humerus.

Penicillin and streptomycin therapy was once again reinstituted but exhibited no favorable effect on the patient's clinical course. No improvement was noted after a therapeutic trial

with digitalis; indeed the ankle edema progressed slightly. Repeated cytologic studies on the sputum were negative for malignant cells and examination of the sputum for acid-fast bacilli was negative. Skin tests for tuberculosis (first strength PPD) and histoplasmosis (1:1000 histoplasmin) were negative.

On the eighteenth hospital day the patient's red blood cell count was 4.1 million, hemoglobin, 12.6 gm. per cent and white blood cell count 6,350; the differential showed 6 per cent eosinophils, 5 per cent stab forms, 70 per cent neutrophils, 15 per cent lymphocytes and 4 per cent monocytes. During the last week of her illness her condition deteriorated rapidly. She remained febrile, became progressively dyspneic and vomited repeatedly. The ankle edema progressed. Despite the administration of fluids parenterally she became dehydrated and disoriented. Repeated examinations of the stool for ova and parasites were negative. An eosinophil count was 55 per $mm.^3$ before and 44 per $mm.^3$ four hours after the administration of corticotropin.

On the twenty-seventh day the patient became comatose, her respirations became irregular and her blood pressure was unobtainable. Nor-epinephrine was administered intravenously, but the patient failed to respond and died on the following day, January 5, 1953.

CLINICAL DISCUSSION

DR. CARL V. MOORE: The history in this case is rather complicated, involving a number of organ systems. The patient had known hypertension for fifteen years and an episode very suggestive of myocardial ischemia or infarction one year before admission. Subsequently signs developed that suggested cardiac insufficiency. For a number of years she suffered from epigastric pain which became very severe in the two months before admission. Just before hospitalization cough, pain in the throat and dysphagia developed. The last two symptoms she attributed to an orange seed which she swallowed and believed had become lodged in her throat. Ten years before admission the patient had had a bilateral oophorectomy and presumably a hysterectomy. Actually, in reading the chart one gets the impression that the patient was not positive that her uterus had been removed, and unfortunately during her hospital stay a pelvic examination was not done. We therefore lack definitive information in this regard. When she entered the hospital, the significant physical findings included an ulcer in the right tonsillar fossa, signs of pulmonary congestion, tenderness over the ribs and upper dorsal spine, cardiac enlargement, hepatomegaly and possible splenomegaly and ankle edema. The laboratory data showed some shift to the left in the differential counts, several abnormal liver function tests—3 plus cephalin-cholesterol flocculation and 29 per cent bromsulphalein retention—and a number of radiologic changes. At this point I should like Dr. Elliott to discuss the latter.

DR. GLADDEN V. ELLIOTT: The first examination of the chest was made on December 11, 1952. At that time there was readily apparent a distinct fine nodulation concentrated in the bases of both lung fields. A possible etiologic factor mentioned in our report was lymphangitic carcinomatosis. Associated with the fine nodulation there was definite calcification of the hilar nodes, particularly on the right. No distinct calcification was seen on the left except possibly in a small parenchymal lesion near the periphery. The appearance of the calcified nodes on the right was not diagnostic. The heart was moderately enlarged, its contour suggesting preponderance of the left ventricle. There were multiple, partially healed fractures, presumably old; there was one in the proximal shaft of the left humerus, several in the ribs along the lateral thoracic margin, and on one of the films, there was a suggestion of an old fracture of a rib on the right. At a subsequent examination on December 24th, thirteen days later, the fine nodulation in the lung was again apparent. There had been no noticeable increase or decrease during the two weeks, and no other significant changes were present. Roentgenograms of the lumbar spine were significant only in that there was a marked degree of hypertrophic arthritis with spurring of the vertebral bodies, and some compression of the second and third lumbar vertebrae without loss of bony substance. There was also wedge-shaped compression of the seventh dorsal vertebra, again without evidence of loss of bony substance. Calcification of the abdominal aorta and marked calcification of the iliac vessels bilaterally was observed. Roentgenographic studies of the esophagus failed to reveal any abnormality. Films of the stomach and duodenum were significant in that they revealed definite splenomegaly with a large soft tissue mass filling the

left upper quadrant and displacing the stomach medially. The liver was also presumed to be enlarged, and extended rather far down into the abdomen. The stomach intrinsically appeared normal. There were good mucosal markings and normal contour except for the displacement by the spleen. The duodenum showed no evidence of displacement, but I need not emphasize that one cannot exclude a retroperitoneal mass on the basis of this observation. A barium enema was performed and the colon was thought to be normal. In summary then, this patient's radiographic findings included nodular lesions in the bases of both lung fields which failed to progress over a period of two weeks, calcification of the right hilum, hepatosplenomegaly, and several changes consistent with the patient's age, namely, arteriosclerosis, hypertrophic osteoarthritis and multiple old fractures which I do not think were associated with metastatic disease.

DR. C. V. MOORE: Dr. Elliott, were the changes in the bones compatible with the diagnosis of osteoporosis?

DR. ELLIOTT: Yes, I think there definitely was evidence of osteoporosis, particularly in the lumbar spine and pelvis.

DR. C. V. MOORE: This woman was in the hospital for about three weeks during which time her course was one of progressive deterioration. She failed to improve after receiving digitalis or antibiotics. Maintenance of nutrition was difficult and she had to be given fluid parenterally. Biopsy of the pharyngeal ulcer was made during her hospital stay but the report of that biopsy is being withheld for the time being. Before taking up the major problems we can dispose of several accessory diagnoses. It seems clear that the patient had osteoporosis and arteriosclerosis. Presumably also coronary artery disease was present. I think we will not discuss these entities further, but rather go on to a consideration of the pulmonary findings. Dr. Goldman, you had an opportunity to review these x-ray films before the conference. Would you begin by discussing the differential diagnosis of the lung lesion?

DR. ALFRED GOLDMAN: In my opinion the pulmonary lesions strongly suggest miliary involvement, and the first diagnosis I would list would be histoplasmosis. I have seen cases of miliary histoplasmosis on a number of occasions, and I believe that the clinical findings in this case are compatible with it. One would also, of course, have to consider miliary tuberculosis. Dr. Elliott suggested lymphangitic carcinomatosis. In my experience it is almost impossible to differentiate roentgenologically between carcinomatosis and miliary infection of the lungs.

DR. C. V. MOORE: You indicate that the patient's clinical course is entirely compatible with histoplasmosis. I presume that you refer to the fact that she had hepatosplenomegaly and a pharyngeal ulcer. When I went over the protocol, the possibility of histoplasmosis also occurred to me, Dr. Goldman, and I looked up various case reports to determine the relative sex incidence of the disease. I was impressed to find that in patients over the age of ten the ratio of the disease in males compared to females is about 8 or 9 to 1. Statistically, therefore, one is on somewhat hazardous grounds if he assumes that histoplasmosis is the most likely diagnosis. Do the statistics lead you to change your opinion?

DR. GOLDMAN: No, I think the combination of hepatosplenomegaly, a pharyngeal ulcer and miliary pulmonary lesions strongly suggest histoplasmosis despite the fact that the disease is much less common in women.

DR. C. V. MOORE: Does the negative histoplasmin skin test dissuade you?

DR. GOLDMAN: No, not at all. There have been a number of cases in this hospital in which patients with proven histoplasmosis have had a negative skin test.

DR. C. V. MOORE: Unfortunately, a complement fixation test was not done. Do you find it to be more reliable in excluding the diagnosis than the skin test?

DR. GOLDMAN: Yes, I would be more dubious about the diagnosis if the complement fixation test were negative, since it is much more accurate. In contrast to the skin test which may be positive and have no significance the complement fixation test is particularly helpful when positive.

DR. C. V. MOORE: Does everyone agree that this patient had histoplasmosis or would someone like to champion another diagnosis?

DR. ALBERT I. MENDELOFF: The chest film looks to me quite suggestive of lymphangitic carcinomatosis. I am impressed by the fact that this patient had tachypnea—when she entered her respiratory rate was thirty-two—and it was noted that she became more tachypneic as her course progressed. This finding is quite characteristic of patients with lymphangitic carcinomatosis.

DR. C. V. MOORE: It is not recorded in the protocol but this woman's vital capacity was only 1,200 cc., about 30 per cent of normal. Dr. Flance, does that information help you in regard to differential diagnosis. Is there more or less depression of vital capacity with miliary pulmonary infections than with lymphangitic carcinomatosis?

DR. I. JEROME FLANCE: I do not believe that one can differentiate between the two on that basis, Dr. Moore. In either case there may be so much interstitial involvement of the lungs that interference with ventilation is marked. In practice one does not usually see vital capacities of that low order in patients with miliary tuberculosis. I have not had enough experience with miliary histoplasmosis to make any comment in this regard, but as Dr. Mendeloff has pointed out, patients with lymphangitic carcinomatosis typically have tachypnea and exhibit marked reduction in vital capacity.

DR. C. V. MOORE: It is possible, then, that the very low vital capacity is more in keeping with lymphangitic carcinomatosis than with miliary infection.

DR. BERNARD A. BERCU: I am impressed by the fact that the pulmonary infiltration was not massive. It is worth while to point out that this patient was an elderly woman with marked kyphosis and much bony change in the thorax. I would suspect that her rib cage was relatively fixed and that the fixation contributed significantly to the low vital capacity.

DR. HARRY L. ALEXANDER: In other words you do not believe that the low vital capacity is necessarily of importance in the differential diagnosis?

DR. BERCU: No, I do not.

DR. C. V. MOORE: Returning to lymphangitic carcinomatosis, Dr. Mendeloff, where do you predict the primary site might be?

DR. MENDELOFF: Almost any tumor can give rise to lymphangitic pulmonary spread, but some tumors can be reasonably well excluded on the basis of the history. Carcinoma of the stomach is most commonly associated with this type of pulmonary involvement, and would certainly be worthy of consideration here in view of the gastrointestinal symptoms. Carcinoma of the pancreas is another tumor which is frequently associated with this type of change. I believe carcinomas arising in the pelvic organs have also been reported in association with lymphangitic carcinomatosis of the lungs, but certainly carcinoma of the stomach and pancreas are the most common ones. It should also be mentioned that primary pulmonary tumors may spread through the lymphatics. Finally, Dr. Moore, this patient may not have had a carcinoma but some other malignant lesion.

DR. C. V. MOORE: Of what particular one are you thinking?

DR. MENDELOFF: Lymphosarcoma comes to mind because of the large liver and spleen and the relative leukopenia.

DR. EDWARD H. REINHARD: I do not believe this patient had lymphosarcoma or lymphoma. One can get miliary infiltration in the lungs with lymphomas but it is quite uncommon.

DR. C. V. MOORE: Recently an interesting report appeared in the *New England Journal of Medicine* summarizing a study of some 2,000 clinico-pathologic conferences reported in that journal over a period of twenty to twenty-five years.[1] The diagnoses most commonly missed were listed, and high on the list was carcinoma of the pancreas. Dr. Scheff, this woman had unexplained epigastric symptoms for many years. Dr. Mendeloff has already pointed out that carcinoma of the pancreas is one of the more common tumors with which lymphangitic carcinomatosis of the lungs is associated. Would you pay serious attention to the diagnosis of carcinoma of the pancreas?

DR. SCHEFF: Yes, I would. It could explain the pulmonary findings and might also explain the hepatosplenomegaly for there may be associated with carcinoma of the pancreas phlebothrombosis of the portal system.

DR. C. V. MOORE: Would you list pancreatic carcinoma as the most likely primary diagnosis?

DR. SCHEFF: Yes, I would.

DR. C. V. MOORE: Dr. Morris Moore of the Barnard Hospital staff is at this conference. He has had considerable experience with histoplasmosis and I should like to ask him whether disseminated histoplasmosis may have a course lasting a number of years with a rather rapid terminal phase. In other words, it is conceivable that many of this patient's symptoms over the last several years could have been due to histoplasmosis, and particularly, is it possible that the epigastric discomfort was related to histoplasmosis?

DR. MORRIS MOORE: Histoplasmosis may exhibit a rather long course with periods of rela-

[1] EDITORIAL, "C.P.C." Clinical analysis or guessing game. *New England J. Med.*, 245: 829, 1951.

tive remission. The epigastric symptoms could indeed be due to the disease for gastrointestinal lesions do occur.

DR. C. V. MOORE: Is there any information to explain the fact that among adults histoplasmosis is far more common in males than in females?

DR. MORRIS MOORE: I know of no explanation for this interesting fact. Most fungus diseases occur equally in males and females.

DR. C. V. MOORE: Is it conceivable that contact with the soil is a factor of importance in the higher incidence in males?

DR. MORRIS MOORE: Although Histoplasma capsulatum has been isolated from soil on many occasions, the portal of entry of the disease is the gastrointestinal tract and patients may be infected by ingesting contaminated foodstuffs, particularly fruits and vegetables. In that case one would not suspect a predominance of cases in the male.

DR. C. V. MOORE: Dr. Wood, are there any antibiotics which are effective in the treatment of histoplasmosis?

DR. W. BARRY WOOD, JR.: There is a drug called ethylvanillate which has been used by Dr. Christie at Vanderbilt on the pediatric service. I believe Dr. Christie considers this compound the most effective one against the fungus. There also was a recent case report in the journal *Antibiotics and Chemotherapy* reporting a favorable result in a patient with histoplasmosis treated with ethylvanillate and propamidine.[2]

DR. GOLDMAN: I talked to Dr. Christie this year and got the impression that he believed that ethylvanillate was a particularly effective drug in infants. Recently he studied a case of terminal histoplasmosis in which a rather remarkable response to ethylvanillate was observed. He and his associates have not, I believe, had any cures in adults. He has no explanation for the relative difference in efficacy of the drug in the different age groups.

DR. MORRIS MOORE: I do not believe the over-all statistics indicate that ethylvanillate is particularly effective.

DR. WOOD: I would agree, Dr. Moore, that the over-all results are not very good but in view of the fact that no other drug works effectively it probably is worth while using ethylvanillate; certainly Dr. Christie's experience suggests that it may be quite effective in the pediatric age group.

DR. C. V. MOORE: Returning to the x-ray films for a moment, I would like to remind Dr. Elliott that when this patient's chest films were originally read, despite the interest of the radiology department in histoplasmosis, that possibility was not raised. As he has stated, however, lymphangitic carcinomatosis was suggested. Dr. Elliott, in retrospect do you believe that the x-ray findings were more suggestive of the latter than they were of histoplasmosis or miliary tuberculosis?

DR. ELLIOTT: I believe Dr. Goldman's earlier comment is pertinent in answer to your question, namely, that in the early stages one cannot differentiate between lymphangitic carcinomatosis and miliary seeding from either histoplasmosis or tuberculosis. Later in the stage of carcinomatosis a more definite reticulation and linear striation appears in contrast to the mottling which seems to be more common in infection. I do not believe that the films afford a basis for definitive differentiation.

DR. WOOD: It seems to me that in the past Dr. Wilson has emphasized that miliary tuberculosis tends to involve the upper half of the lungs whereas in histoplasmosis the lesions tend to be in the lower half. Has that been your experience, Dr. Elliott?

DR. ELLIOTT: I have not had enough personal experience to be certain, Dr. Wood. Both lesions are relatively rare but we have seen more histoplasmosis than miliary tuberculosis recently. Dr. Wilson's impression agrees with that of several other radiologists.

DR. GOLDMAN: It is my impression that the correlation between histoplasmin and tuberculin skin tests with miliary calcification suggests that in tuberculosis the lesions are in the upper portion of the lung and those of histoplasmosis in the lower portion.

DR. C. V. MOORE: In the report by Parsons and Zarafonetis summarizing seventy-one cases of histoplasmosis[3] it is strongly emphasized that hyperglobulinemia is a common feature of the disease. Furcolow makes the same point, based on observations in sixteen patients in whom histoplasmosis was diagnosed during life.[4] You

[2] ELLIS, F. F., JR., SCOTT, R. J. and MILLER, J. M. Treatment of progressive disseminated histoplasmosis with ethylvanillate and propamidine. *Antibiotics & Chemother.*, 2: 347, 1952.

[3] PARSONS, R. J. and ZARAFONETIS, C. J. D. Histoplasmosis in man. *Arch. Int. Med.*, 75: 1, 1945.

[4] FURCOLOW, M. L. Further observations on histoplasmosis; mycology and bacteriology. *Pub. Health Rep.*, 65: 965, 1950.

will remember that this patient had a normal albumin-globulin ratio. Thus there are at least two significant points, namely, the sex incidence and the incidence of hyperglobininemia, which militate against the diagnosis of histoplasmosis in this case.

DR. GOLDMAN: Those two points are important but in an individual instance statistics may be misleading. Conversely, we have seen many cases in which there has been a significant reversal of the albumin-globulin ratio never satisfactorily explained.

DR. C. V. MOORE: Dr. Wood told me just before the conference that he believed the patient also had histoplasmosis. In addition to the two points which I already mentioned I should have referred also to the negative skin test. Although we are all aware of the fact that patients with histoplasmosis may have negative histoplasmin tests, in the sixteen cases reported by Furcolow the test was negative in only three, the rest having been positive at least at some time during their course.

DR. WOOD: The only thing which really bothers me is the absence of hyperglobulinemia. The fact that the histoplasmin skin test is negative does not dissuade me at all since in some stages of the disease the skin test is commonly negative. The sex incidence, as has been pointed out, is against the diagnosis but in an individual case is relatively unimportant. I am strongly influenced by the presence of the pharyngeal ulcer. It would be difficult to explain on any other diagnosis except perhaps a malignant lesion, and apparently serial observation of the ulcer led the otolaryngologist who saw the patient to state that the ulcer was not malignant. It is extremely common to see such ulcerative lesions in patients with histoplasmosis, so that all in all I conclude that this patient had that disease.

Dr. C. V. MOORE: Would anyone care to support the alternative diagnosis of miliary tuberculosis? Dr. Skilling, how do you feel about it?

DR. DAVID SKILLING: I do not think miliary tuberculosis would be likely. I have been particularly impressed by the aforementioned fact that tuberculosis usually involves the upper portion of the lungs.

DR. BERCU: The possibility that this woman suffered from adrenal insufficiency terminally is suggested by the fact that her serum sodium was low, her blood pressure fell and she failed to respond to corticotropin. If she did indeed have adrenal insufficiency it would favor histoplasmosis. Was there any other evidence suggesting adrenal failure in the record?

DR. C. V. MOORE: No, the only points in its favor were those you mentioned.

DR. MENDELOFF: I should like to ask for some information. The patient's white count was relatively low and remained essentially stationary throughout the course of her disease. Is that characteristic of histoplasmosis? It was my impression that the white count was usually higher.

DR. C. V. MOORE: Variations in total leukocyte counts are so great that they usually have little diagnostic value. Furthermore, leukopenia is not unusual whenever splenomegaly exists. Late in the first week of hospitalization the patient had a chill and a temperature elevation to 40°C. These findings developed about four or five hours after she had received an infusion of 5 per cent glucose in water and conceivably could have been due to a pyrogenic reaction. The house officer who saw her, however, thought that she had pneumonia and was much worried by the fact that there was no further shift in the differential or elevation of the white count. In any case the fact that the white count did not go any higher is not of much help in the differential diagnosis.

A PHYSICIAN: In the protocol it was stated that later in the patient's course a compression factor of the seventh dorsal vertebra was reported by the radiologist. This finding was not mentioned as being observed in the metastatic series obtained when she first entered the hospital. Is this significant?

DR. ELLIOTT: No, I do not think so because the first lateral view was taken at the time of the "later" examination to which you referred. There was no lateral view of the dorsal spine taken with the metastatic series.

DR. C. V. MOORE: Are there any other comments?

DR. MENDELOFF: I believe a word may be said about the hepatic function tests reported here. They represent a pattern not uncommon with neoplastic involvement of the liver. The changes are not specific but the occurrence of bromsulfalein retention without an increase in bilirubin, and slight elevation of the alkaline phosphatase is a combination most frequently found in metastatic liver disease.

DR. ROBERT J. GLASER: As a point of information, would Dr. Robert Moore say something about malignant lesions which involve the pharynx? Are they apt to metastasize widely?

DR. ROBERT A. MOORE: In the region in which the ulcer was described one might expect a transitional cell or epidermoid carcinoma or the tumor which is called by some pathologists lymphoepithelioma. The latter usually give rise to large metastatic lesions in the neck. As far as I know, tumors of the pharynx are not apt to extend to the lung unless they also involve the nodes in the neck. Were the cervical lymph nodes enlarged?

DR. C. V. MOORE: No, they were not.

DR. ROBERT A. MOORE: In that case I would not think that it was very likely that the pulmonary lesion could be explained on the basis of a malignant lesion in the pharynx.

DR. HARRY L. ALEXANDER: It seems to me that if the ulcer in the pharynx played an important part in this disease two diagnoses must be seriously considered—(1) histoplasmosis and (2) lymphosarcoma. Primary lymphosarcoma of the pharynx commonly ulcerates but I would expect enlarged cervical lymph nodes in that instance.

DR. SCHEFF: What about the lack of anemia in a patient with histoplasmosis?

DR. REINHARD: Patients with miliary histoplasmosis or tuberculosis become anemic if they suffer from either disease long enough. The same thing would be true of patients with miliary carcinomatosis. The absence of anemia, however, does not seem to me to be of importance in the differential diagnosis. I would merely assume that it indicated that the disease had not gone on long enough to produce anemia.

DR. SCHEFF: The reason I ask the question is that a number of patients I have seen with carcinoma of the pancreas do not seem to develop anemia very rapidly.

DR. C. V. MOORE: I think Dr. Scheff's point is a good one. Most of the patients with widely disseminated histoplasmosis do develop at least a moderate degree of anemia. In summary, I think that the majority opinion favors the diagnosis of histoplasmosis but lymphangitic carcinoma of the lungs due to carcinoma of the stomach or of the pancreas has been suggested and miliary tuberculosis also has been considered. I do not believe that Dr. Harold Joseph is here but he was the assistant resident who took care of this patient when she was in the hospital. In collaboration with Mr. Ray in the Bacteriologic Laboratory he identified Histoplasma capsulatum in the saliva of this patient,

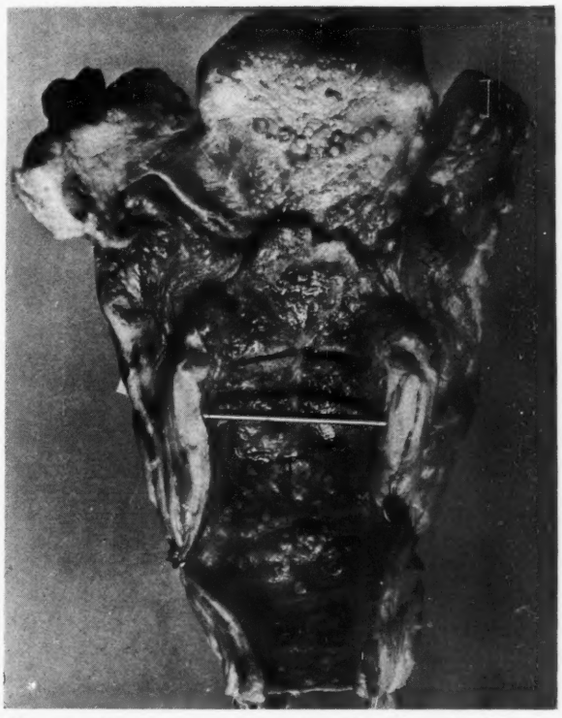

FIG. 1. The larynx and trachea showing the discrete elevated and ulcerated lesions on the mucosa.

and shortly thereafter the pharyngeal biopsy was reported as positive for histoplasma. These findings obviously lend strong support to the diagnosis of disseminated histoplasmosis, but the disease could have been localized and the dissemination due to another process.

Clinical Diagnoses: Histoplasmosis; ? carcinoma of the pancreas or stomach; ? miliary tuberculosis.

PATHOLOGIC DISCUSSION

DR. WILLIAM R. MURPHY: The gross anatomic findings confirmed the presence of an ulcer in the pharynx (Fig. 1) together with extensive acute necrotizing ulceration of the epiglottis, the trachea and some of the major bronchi. These were isolated, elevated and necrotic lesions with relatively normal mucosa between them. A single palpable lymph node was present at the angle of the right mandible. It was extremely firm and on cut section was white and fibrous. In the lung there were no nodules such as one associates with a granulomatous infection, yet there was an irregular type of consolidation in the lower lobes and mucopurulent material could be expressed from the bronchi. The adrenals (Fig. 2) were enlarged to about 60 gm. each and were grossly caseous. In

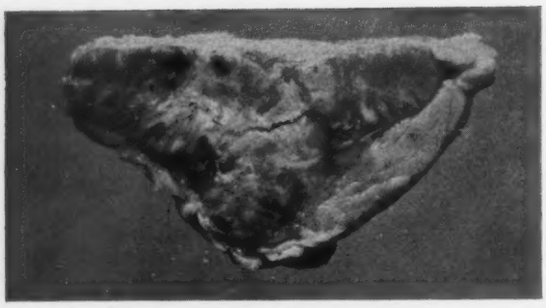

FIG. 2. A gross section of the adrenal with massive enlargement and total replacement of the adrenal tissue by caseous necrosis.

the intestine there were lesions not unlike those seen in the trachea and bronchi except that they obviously involved the solitary lymph follicles. Quite aside from this group of lesions there was arteriosclerosis of an advanced grade involving most of the blood vessels of the body and associated with hypertrophy of the heart which weighed 360 gm. in a woman who herself weighed but 60 kg. There was edema of the lower extremities and gross evidence of passive congestion of slight grade in the liver, spleen and kidneys, but there was no excess fluid in the serous cavities.

DR. R. A. MOORE: The first microscopic preparation, Figure 3, is of the cervical lymph node beneath the angle of the right mandible. It contains numerous giant cells scattered throughout the rather dense connective tissue that replaces the normal stroma of the node. Despite the fact that the diagnosis of histoplasmosis had been established by examination of the biopsy of the ulcer in the pharynx, we were not able to identify histoplasma in this lesion. This same type of lesion is present throughout the body with or without demonstrable organisms and is probably a granulomatous reaction to their presence. This lymph node is important in evaluating the pathogenesis of the history in this case, inasmuch as it is a lesion in which most of the lymphoid tissue has been destroyed and replaced by fibrous tissue. Assuming it is a single disease which involves this lymph node, and I see no reason for not accepting that, then we must conclude that there has been disease in this lymph node for many months in order to bring about the total destruction and replacement by fibrous tissue. This indicates that this woman did not have histoplasmosis as just a terminal event in her life, but rather that it had been there for a considerably longer time than the three weeks indicated by the history of symptoms referable to the pharynx.

Figure 4 illustrates a higher magnification of the giant cells and minute foci of necrosis in lymphoid tissue which were characteristic of the disseminated lesions in the cervical node and elsewhere in the body. The section of the biopsy of the pharyngeal ulcer was reported as showing superficial necrosis over an underlying inflammatory reaction with numerous and prominent thick-walled, small blood vessels running through a heavy infiltrate of mononuclear cells and lymphocytes in a stroma of swollen, active fibroblasts. Such thick-walled sinusoids or capillaries and an inflammatory reaction of mononuclear type are characteristic of subacute inflammation that is of some duration in time. Periodic acid-Schiff stains on this material were successful in demonstrating numerous Histoplasma capsulatum in these ulcers.

At autopsy cultures were made of the tracheal ulcers and four organisms were obtained: Histoplasma capsulatum, Micrococcus pyogenes, var. aureus, Escherichia coli and Candida albicans. We could identify with relative ease in the tissue in direct association with the lesion histoplasma and gram-positive cocci, but no evidence could be found in the sections of gram-negative bacilli or any fungi of the candida group. This combination of bacterial and histologic findings illustrates a point in evaluating the importance of organisms that might be obtained from postmortem material. Particularly when the lesions are on a surface exposed to the environment, the organisms isolated by bacteriologic culture do not always represent the causative organisms. Conclusive demonstration of the etiologic role of an organism should include its identification in the tissues associated with the lesions. In the particular lesions of this case the absence of gram-negative bacilli and candida in the sections leads us to discount their importance and to classify them as contaminants. The cocci and histoplasma, however, were intimately admixed with the inflammatory exudate. The cocci were superficial and associated with an infiltration of polymorphonuclear leukocytes in the necrotic layers. This finding clearly suggested that they had been added to the surface above the basically mononuclear reaction characteristic of histoplasmosis as seen deeper in the ulcer and in the other organs of the body.

Sections of the adrenal, as shown in Figure 5,

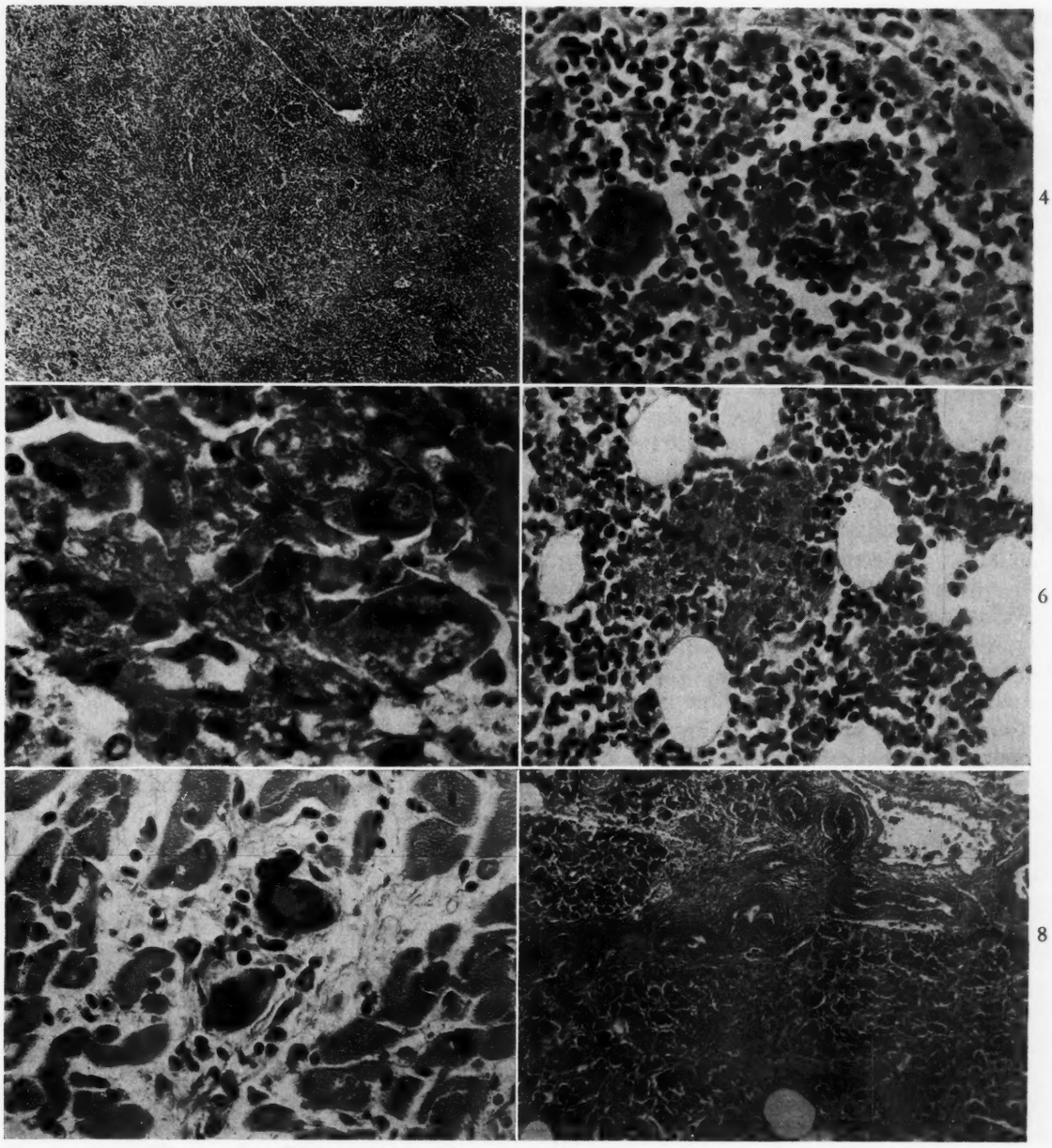

FIG. 3. A low magnification of a cervical lymph node with diffuse fibrosis, giant cells and generalized granulomatous reaction.

FIG. 4. Giant cells and minute foci of necrosis in lymphoid tissue in the cervical lymph node.

FIG. 5. Necrosis with heavy parasitism of cells by Histoplasma capsulatum in the adrenal.

FIG. 6. A small focus of necrosis and granulomatous reaction in the bone marrow in which Histoplasma capsulatum could be identified.

FIG. 7. A microscopic granuloma in the myocardium consisting essentially of giant cells and a few mononuclear cells. Similar granulomas were present in the liver, peri-aortic lymph nodes and pancreas, but no organisms could be found within them.

FIG. 8. Pancreas, with fibrous thickening of interstitial septa, thickening of small arteries and a light infiltration of mononuclear cells interpreted as a diffuse pancreatitis incidental to the histoplasmosis.

show extensive necrosis with peripheral granulomatous reaction and the persistence of only a small amount of cortical cells. Throughout the viable granulomatous tissue there are numerous organisms that are easily identified in sections. Cultures of this material, however, yielded no organisms although they were performed in exactly the same manner as were cultures of the pharyngeal ulcer, the bronchial secretions and the blood, which were positive for Histoplasma capsulatum. Figures 6 and 7 illustrate the microscopic granulomas of mononuclear cells, tiny amounts of necrosis and giant cells, which are found scattered throughout the bone marrow, myocardium, liver, periaortic lymph nodes, and in a few foci in the pancreas. Histoplasma organisms can be identified in the small granulomas in the bone marrow which is compatible with the clinical experience that the definitive diagnosis can often be made from bone marrow punctates. The small granulomas in the other tissues are undoubtedly part of histoplasmosis, as we have observed them in many cases; however, we have never been successful in finding the organisms in granulomas of the type illustrated in Figure 7. This section of the myocardium is particularly interesting in that this is one of the few cases in which we have observed involvement of that tissue. This patient also had an advanced degree of coronary arteriosclerosis, but there was no effect of that disease on the heart muscle in terms of destruction of muscle fibers or fibrosis.

Sections of the lungs showed many alveoli and smaller bronchi filled with an exudate composed very largely of polymorphonuclear leukocytes with a few threads of fibrin. We did not find in any of the material from the lungs that we examined microscopically any significant granulomatous lesions. Bacteriologic and periodic acid-Schiff stains showed gram-positive cocci in association with the alveolar exudate, but no histoplasma could be identified.

The final section, Figure 8, is of the pancreas in which there are obviously thickened small arteries and widening of the septa by increased amounts of fibrous tissue causing a lobulation of the pancreas. There is also a light infiltration of a few mononuclear cells, but no leukocytes in the interstitial connective tissue. Only a very few small granulomas such as those seen in the liver were identified in the pancreas and apparently this diffuse reaction of the interstitial tissue represents an independent subacute and chronic pancreatitis of slight degree not related to the fungus.

It is apparent that the principal diagnosis in this case is disseminated histoplasmosis with massive involvement of the adrenals causing marked caseation and loss of most of the glandular substance. There is a lesion of the pharynx which has been there for some time and is associated with involvement of the regional lymph nodes and fibrosis, and then acute ulceration which spread into the lower portion of the trachea and bronchi and into the intestines. The lesions in the intestine are acute with necrosis and an inflammatory reaction and histoplasma are identifiable in the tissues. In addition, this patient had cardiovascular renal disease in terms of advanced arteriosclerosis, slight arteriolar nephrosclerosis, and hypertrophy of the heart. There is not, however, much evidence that heart failure made any great contribution to the clinical picture. The long-standing abdominal pain is not clearly explained by the anatomic findings, except for the possibility that the relatively slight degree of chronic interstitial pancreatitis was responsible for this symptom. Despite the fact that roentgenographic changes which were interpreted as compatible with disseminated histoplasmosis had been observed for at least three weeks, the lesions at autopsy in the lungs are apparently only those of bronchopneumonia. We do not find any granulomatous lesions that can be called histoplasmosis and it does not seem likely that the terminal bacterial infection could have erased changes that had been responsible for such a clear x-ray picture, or that any great difficulty might be expected in encountering granulomas responsible for such a change.

Final Anatomic Diagnoses: Histoplasmosis, involving the pharynx, larynx, trachea, bronchi, adrenals, small intestine and colon; microscopic granulomas in the myocardium, liver, pancreas, peri-aortic lymph nodes and bone marrow; bronchopneumonia.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Asbestosis and Bronchogenic Carcinoma*

Report of One Autopsied Case and Review of the Available Literature

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Boston, Massachusetts

THERE are several reasons for presenting in detail a case report and a review of the available literature dealing with the relationship between occupational exposure to asbestos and respiratory tract malignancy. The apparent increase in bronchogenic carcinoma, especially in males, reported in the past decade has led to scrutiny of respirable dusts as possible etiology. Most English observers[1–3] are satisfied that there is a statistically significant increase in pulmonary malignancy among asbestos workers. Some American writers consider that the experience to date does not support this contention.[4,5] The work of Graham,[6,7] Doll and Hill,[8] and Ochsner[9,10] has created much interest in the correlation of cigarette smoking with bronchogenic carcinoma. E. R., whose case is herein presented, was exposed to harmful amounts of asbestos dust and was a chain smoker. This provides speculation as to the possible role of two etiologic agents.

Few reported cases of lung cancer related to industrial asbestos exposures provide data on the character and quantity of dust exposure. This is a serious deficit in exact study of etiologic correlation. In the clinical report presented herein State authorities have determined by measurement that the asbestos dust exposure of this man during his twelve years of work was considerably above the safe level, which is considered to be five million particles per cubic foot of air for an eight-hour working day.

It is pertinent to this presentation that there are probably about 10,000 workers engaged in potentially hazardous asbestos manufacturing operations in the United States.[11] Middleton reports the number in Great Britain as between 3,000 to 5,000.[12] Most of the industry is engaged in asbestos textile manufacturing producing insulating mattresses, brake linings, fire proof curtains and clothing. The chief operations are disintegration of the crude mineral, carding the fiber, separating the more useful long from the short fiber, spinning, plaiting and weaving the asbestos, often with cotton. Insulating material is produced by mixing magnesia, diatomaceous earth and other materials with asbestos to make cements or fillings for insulating boilers, engines and pipes. Other non-textile asbestos products so made include asbestos cement, sheets, brake and clutch linings, electrodes and switchboard panels.

Asbestos is a hydrated magnesium silicate. The chief supplies are in Canada, Cape Province, Italy, Rhodesia and Russia. Asbestos dust given off in manufacturing processes consists of fragments of fibers and small rounded or angular particles. Actual studies in industry show the size and shape of the particles of asbestos to be such as may gain entrance into the bronchioles.[14] Experience has led to the acceptance of five million particles of asbestos per cubic foot of air, of small enough size to be respirable, to be the safe working concentration.

Some operations because of their dustiness are more hazardous than others in asbestos manufacturing. Bagging the asbestos, separating the long from the short fibers, carding, spinning and weaving show a greater statistical evidence of asbestosis than do other operations. As might be expected, the longer the duration of exposure the greater the number of cases. In the Merewether and Price series there was one case under four years' exposure, and up to 53.6 per cent with fifteen to nineteen years' exposure.[15]

CASE REPORT

E. R. (MGH #735586),[16] a forty-one year old asbestos mill worker, entered the Massachusetts General Hospital in April, 1951. The chief

* From the Departments of Medicine and Pathology, and the Occupational Medical Clinic, Massachusetts General Hospital, Boston, Mass. This work was supported in part by the National Institutes of Health, Division of Research Grants.

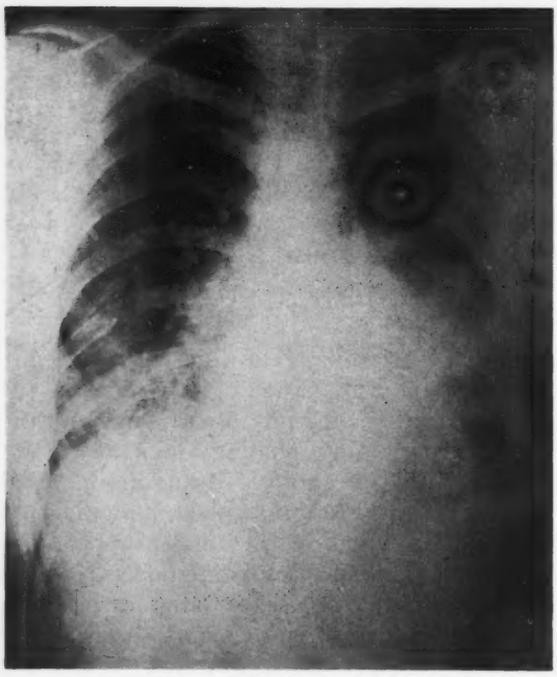

FIG. 1. X-ray of chest. The lower lobes are reduced in size and show a "honeycomb" pattern. There is an increase in linear and nodular markings. A density is seen in the region of the lingula with enlargement of lymph nodes in the left lung root, suggesting a tumor in that area.

complaint was progressive low back pain which had been present for four months and was only partially relieved by aspirin. In addition, one month before admission the patient noticed increasing dyspnea on exertion, a worsening of his chronic productive cough, night sweats, anorexia, feverishness and a 10-pound weight loss. He had worked in an asbestos mill for about twelve years but had stopped working there for two years prior to this hospital admission. In the mill he had spent one year in the "picker room" where crushing, grinding and sorting of long asbestos fibers was carried out. He also worked five years in the carding room where the concentration of fibers had been determined by authorities to be considerably above the safe level. He used one can of snuff and smoked on an average of one to two packs of cigarettes daily for many years. For seven or eight years he had been aware of clubbing of his fingers; one flight dyspnea was present for about two years. There had been no hemoptysis.

Physical examination revealed a chronically ill and dyspneic man with evidence of weight loss and cyanosis of the lips and nail beds. The blood pressure was 110/75, pulse 96, respirations 30, and temperature 99°F. orally. His chest was thin and showed poor expansion. There were dullness and reduced breath sounds at both lung bases with sticky inspiratory crackling rales over the region of the left lower lobe. The left border of cardiac dullness was 10 cm. to the left of the midsternal line in the fifth interspace; there were occasional extra systoles; P_2 was greater than A_2; there was some pulsus paradoxus. Liver and spleen were not felt. There was tenderness of the spine over L-4 with spasm of the lumbar musculature. He had extreme clubbing of fingers and toes.

TABLE I

PULMONARY FUNCTION STUDIES* BEFORE AND AFTER ACTH†

	Before ACTH	After ACTH	Approximate Normal Values‡[30]
Vital capacity (L.)	2.4	2.18	3.9
Maximum breathing capacity (L./min.)	52.5	79.5	105
Residual volume (L.)	1.575	1.49	1.30
Effective alveolar ventilation (L./min.)	7.63	5.48	5.02
Alveolar pO_2 (mm. Hg)	115.0	105.0	105–107
Arterial pO_2 (mm. Hg)	88.0	76.0	95–97
Arterial pCO_2 (mm. Hg)	36.0	42.0	40–43
Arterial O_2 saturation (%)	97.3	94.4	95–97
Serum pH	7.45	7.42	7.39
Alveolar-arterial O_2 difference (mm. Hg)	27.	29.	10.

* These studies were performed by Dr. John Affeldt, Department of Physiology, Harvard School of Public Health.

† ACTH 100 mg. intramuscularly for ten days.

‡ Body surface area was 1.62 sq. m.

Laboratory data revealed a normal urinalysis. Hemoglobin was 14.0 gm. per cent and the white count was 5,700, with a normal differential. Chest x-ray revealed the lower lobes reduced in size and showing a honeycomb pattern. (Fig. 1.) There appeared to be a homogenous density in the lingula with enlargement of lymph nodes in the left lung root suggesting a tumor in the region of the left lower lobe. Films of the spine indicated areas of increased and decreased density in the fourth lumbar vertebra giving the appearance of metastatic malignancy. Electrocardiogram showed non-specific T wave changes. Non-protein nitrogen was 27 mg. per cent, CO_2 29.4 mEq./L., alkaline phosphatase 4.9 Bodansky units. Repeated examinations of the sputum were negative for acid-fast organisms, asbestosis bodies and malignant cells. Two bronchoscopies revealed obstruction of the left lower lobe bronchus. The patient was given a trial of ACTH 100 mg. daily intramuscularly

for ten days. Clinically there was no change except for euphoria. Pulmonary function and cardiac catheterization studies were performed before and after ACTH and likewise showed no significant changes. (Tables I and II.) Cardiac catheterization did reveal chronic cor pulmonale with slight pulmonary hypertension; after exercise the pulmonary hypertension increased and significant arterial oxygen unsaturation appeared.

TABLE II

CARDIAC CATHETERIZATION STUDIES* BEFORE AND AFTER ACTH†

	O_2 Consumption (cc./min./ sq. m.)	O_2 Capacity Radial Artery (cc./100 cc.)	O_2 Content Radial Artery (cc./100 cc.)	O_2 Saturation Radial Artery (%)	Pulmonary Artery Pressure (mm. Hg)	Mean Pulmonary Artery Pressure (mm. Hg)	Cardiac Index (L./min./ sq. m.)
Approximate normal values[30]	145	20.0	19.0	96	30/10	15	3.2
Before ACTH: Rest	180	19.3	18.1	94	36/14	21	4.47
Before ACTH: Mild exercise (2 min.)	370				43/14	28	5.55
After ACTH: Rest	156	17.4	16.6	95	38/15	23	4.02
After ACTH: Mild exercise (2 min.)	349				52/22	36	6.97

* These studies were performed by the Cardiac Catheterization Unit of the Massachusetts General Hospital, including Drs. G. S. Myers, A. L. Friedlich, J. R. O'Neill, G. Cohen and J. G. Scannell.

† ACTH 100 mg. intramuscularly for ten days.

Before discharge from the hospital he received radiation (1,200 r) to the lumbar spine with no relief of the back pain.

For several weeks after discharge the patient seemed somewhat better and returned to light work. However, the cough increased markedly and he had severe dyspnea at rest so that after two months he had to be readmitted. Physical examination on re-entry revealed a temperature of 100.4°F. rectally, pulse of 120-144, respirations 30 per minute. He had marked tachypnea, moderate cyanosis and such dyspnea that it was very difficult for him to speak. There were many inspiratory and expiratory wheezes throughout the lung fields. At the right base there were moist bubbling rales together with dullness, reduced tactile fremitus and increased vocal fremitus. The left border of cardiac dullness now extended out 12 cm. from the midsternal line. P_2 was much louder than A_2. The liver was percussed down two and a half fingerbreadths and there was 2 plus ankle edema. At this time the white blood count was 6,500, hemoglobin 11.5 gm. per cent.

It was believed that the patient had pneumonitis in the right lower lobe and early cor pulmonale with congestive failure. He was digitalized, given mercurial diuretics, antibiotics (penicillin and streptomycin), and was in an oxygen tent most of the time. Chest x-rays now were suggestive of lymphatic spread of tumor. In spite of all therapeutic measures fever, dyspnea and cyanosis grew worse. He became confused and died on the thirty-fourth hospital day.

At necropsy the patient was emaciated; the thorax was lengthened in the anteroposterior diameter. There was clubbing of the fingers and toes.

On opening the thorax the lungs did not collapse but remained inflated, completely filling both pleural cavities. The majority of the pleural space was obliterated bilaterally by dense fibrous adhesions between the visceral and parietal layers. Both the visceral and parietal pleurae were markedly thickened, gray fibrous membranes measuring up to 0.3 cm. thick. There were 100 cc. of clear straw-colored fluid loculated in the left base. The interlobar fissures were obliterated by fibrous tissue. Scattered throughout the adherent layers of the diaphragmatic pleura, especially on the right, were a number of whitish gray, shiny plaques 0.5 cm. long; these resembled similar plaques

FIG. 2. Cut surface of left lung after formalin fixation. Note diffuse pulmonary fibrosis and marked pleural thickening which obliterates the interlobar fissure.

FIG. 3. Asbestosis bodies in the lung. The club-shaped, beaded asbestosis bodies are seen in the alveolar ducts, surrounded by macrophages and "dust cells"; × 900.

seen on the upper surface of the liver, to be described. The lungs weighed 2,710 gm., were voluminous and very firm throughout; no discrete nodules could be felt. (Fig. 2.) Multiple sections showed a uniform brownish gray surface throughout except in the left lower lobe where there appeared to be a diffuse marked fibrosis throughout the parenchyma. The left lower lobe bronchus was completely occluded 1 cm. from its origin by pinkish gray, firm tissue for a distance of 1.4 cm.; here the bronchus measured 0.7 cm. in diameter; the firm pinkish gray tissue extended into the parenchyma for a distance of 1.7 cm. Similar tissue extended from this point in the bronchus to the pleura and into the wall of the left atrium which was adherent to the pleura at this point; the gross atrial involvement measured 2.3 by 0.7 cm. in extent. The upper lobe bronchi were rigid and narrowed by a thick, white fibrous coat. The right lower and to some extent the right middle and left lower lobe bronchi were dilated, and there was collapse of the intervening parenchyma. The veins and arteries appeared normal.

There were adhesions between the visceral and parietal pericardium both at the apex and the base. The apical adhesions were thin fibrous strands but those at the base were extensions of the firm tissue described in the left lower lobe bronchus. The heart weighed 360 gm. There was involvement of the left atrium and auricle by thick, firm, grayish pink tissue for an area measuring 2.3 by 0.7 cm. The remaining myocardium appeared uninvolved and measured 0.6 cm. thick in the right ventricle, 1.3 cm. in the left. The endocardium and valves were negative.

The diaphragms contained firm grayish pink areas of plaque-like thickening which measured up to 0.5 cm. in diameter. These were seen on both the pleural and peritoneal surfaces, were apposed and loosely adherent to similar confluent areas in Glisson's capsule. The remaining organs, with the exception of the fourth lumbar vertebra, were negative. This vertebra appeared opalescent and resembled marble, but its consistency was softer than the adjacent vertebrae. The body appeared to have increased porosity.

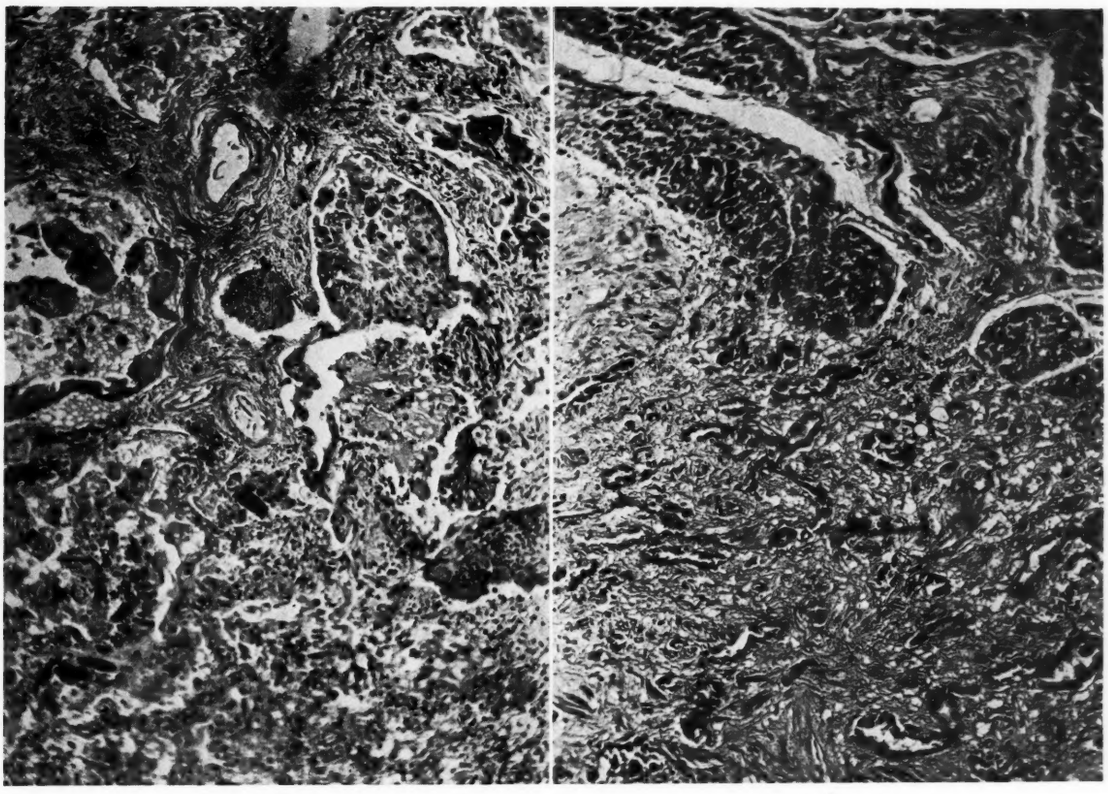

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FIG. 4. Squamous metaplasia in the alveolar ducts; note also asbestosis bodies and interstitial fibrosis; × 100.

FIG. 5. Adenocarcinoma invading the myocardium; × 100.

The lungs were sectioned topographically; sections from all segmental bronchi were taken near the hilum, the mid-lobar and the peripheral areas. These basic histologic patterns could be seen:

Fibrosis: Throughout the lungs there was proliferation of fibrous tissue around the bronchi, the arteries, alveolar ducts; the interlobar septa and pleurae were also thickened. There was peribronchial and alveolar duct fibrosis in both apices, and slight alveolar wall thickening as demonstrated by connective tissue stains. The fibrosis increased in the remaining portions of the lungs, was heaviest in the hilar and mid-lobar areas but extended to the periphery. This confirmed the gross impression of diffuse fibrosis.

Asbestosis bodies: Asbestosis bodies were present in all sections. (Fig. 3.) These were segmented fibers averaging 50μ long, some straight and some club-shaped, others resembled dumb bells which stained dark brown on hematoxylin-eosin preparations, and blue on Prussian blue (iron) preparations. Particles of iron-staining dust and larger, easily identifiable asbestosis body particles, were present in the macrophages. The distribution was equal bilaterally, being slight to moderate in the apical segments, quite marked in the remainder of the lung and occurring with equal intensity in the hilar, mid-lobar and peripheral zones.

While most of the asbestosis bodies were seen in the bronchioles and alveolar ducts, a few could be seen in the alveoli, and fragments were found both in the macrophages and in the lymphatics. Several aggregations of asbestosis bodies were found in the bronchi. Fragmented asbestos fibers were found mostly in the macrophages but occasional iron-staining particles were found free on the alveolar walls. Much, but by no means all, of this material in the macrophages took the iron stain.

Inflammatory response: The chief inflammatory cells responding to the irritant were the macrophages. These cells were seen in abundance in every section; they lined up along the walls of the alveolar ducts, filled the lumina of bronchioles and alveoli, and were found throughout the septa and fibrous tissue. Most of these con-

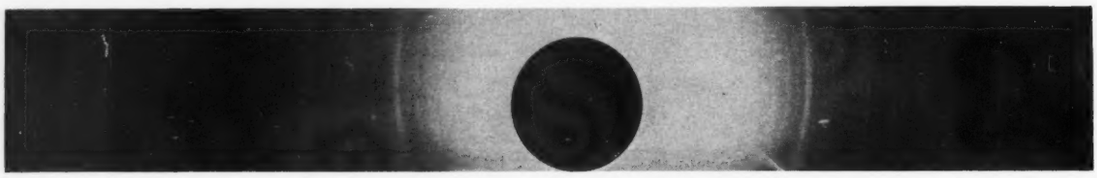

FIG. 6. X-ray diffraction film of lung residue of E. R.* The lines listed when compared to the known pattern for asbestos give positive proof that the lung residue is essentially asbestos.

Table of "D" lines:

4.52	2.42	1.61
4.20	2.38	1.531
3.35	2.115	1.49
2.98	1.84	1.44
2.67	1.70	1.38

* A 68.5 gm. sample of formalized lung tissue was digested in 20 volumes hydrogen peroxide, the digestion being accelerated with gentle heating. The residue from the digestion was treated with dilute hydrochloric acid, filtered, washed and ignited at 500°F. The ignited residue was analyzed by x-ray diffraction by the method described in the article by Hanawalt, J. D., Rinn, H. W., Frevel, L. K., "Chemical analysis by x-ray diffraction," *Indust. & Eng. Chem., Anal. Ed.*, vol. 10, no. 9, 1938. This work was done by R. I. Chamberlin and A. Woewucki, Jr. of the Massachusetts Bonding and Insurance Company, Boston, Mass.

tained brown pigment granules many of which took an iron stain, and portions of asbestosis bodies were also found in the macrophages. (These cells have been called dust cells and are thought to lay down the iron on the asbestos fiber, constituting the asbestosis body.) Anthracotic pigment was also present in the macrophages. Multinucleated giant cells of the foreign body type were found in abundance in all areas; many of these contained birefringent asteroidal bodies. Few lymphocytes were seen; those present were scattered around the bronchi near the hila. A few focal areas of bronchopneumonia with polymorphonuclear infiltration were present; these had no particular relation or location to any grouping of the asbestosis bodies and were undoubtedly a terminal phenomenon.

Throughout the lungs many air sacs were dilated and contained a granular eosinophilic material, probably fibrin. Some of these plugs were undergoing organization, mainly in alveolar ducts; this type of fibrosis probably accounts for a small percentage of the total fibrosis seen.

Bronchi: The bronchi of the lower lobes showed marked bronchiectasis; there was dilatation, fibrosis of the muscular coat and peribronchial fibrosis. While the latter was most marked in the lower lobes it was seen in the hilar and midzonal regions of almost all segments. Another striking feature was widespread squamous metaplasia of the bronchial epithelium. (Fig. 4.) This was most marked in the alveolar ducts; it was found in all areas and was not particularly related topographically to the adenocarcinoma described later.

Blood vessels: The arteries and arterioles of the right middle and both lower lobes showed moderate intimal thickening with hyalinization and narrowed lumina. This was most marked near the hila but was found occasionally farther into the periphery.

Tumor: Adenocarcinoma was found originating in the inferior lingual segment of the left upper lobe bronchus. The tumor was present in the mid-zonal area of the apical posterior segment of the left upper lobe, the entire lingula and left lower lobe, as well as the right middle and lower lobes. It had spread by submucosal and lymphatic routes. Sections of the left atrium showed direct extension through the left hilum into the pericardium and myocardium. (Fig. 5.) Metastatic tumor was seen in the fourth lumbar vertebra.

Asbestos "granulomas": The white plaques described in the diaphragm and Glisson's capsule were made up chiefly of hyalinized connective tissue. No asbestosis bodies or giant cells were seen. These distinctive areas grossly suggested granulomas.

X-ray diffraction studies were carried out on a sample of formalized lung tissue. The resulting pattern indicated that the lung residue was mostly asbestos. (Fig. 6.)

COMMENTS

Asbestosis may be defined as a specific occupational disease caused by the inhalation of asbestos fibers and leading to a progressive fibrosis and scarring within the lungs.[17] It has been demonstrated by Gardner[20] and again by

Vorwald[18] that usually the disease will not occur with fibers less than 20μ in length or a concentration below five million particles per cubic foot of air.

The pathologic processes resulting from the inhalation of asbestos particles are believed to be due not to their chemical nature but, rather, the consequence of mechanical irritation from fibers lodged in the respiratory tree.[18–20] The inhaled particles are, in general, too large to pass beyond the respiratory bronchioles and so they remain there to initiate a foreign body reaction which eventually leads to fibrosis.[21] The pathologic sequence of events can be considered as occurring in three stages: (1) desquamation and exudation, (2) formation of asbestosis bodies and (3) fibrosis and scarring.

The long fibers traumatize the epithelial cells lining the smaller bronchioles and the constant irritation and friction cause the cells to desquamate. Macrophages pour forth in an effort to phagocytize the fibers. In our case fragmented asbestosis bodies were also seen within macrophages and lymphatics. A second reaction to the asbestos fiber in the lung is the production of the so-called "asbestosis body."[22–24] This results from a reaction occurring between the asbestos particle and surrounding tissues. It is a thickening of the fiber due to the deposition along its course of a protein matrix containing iron which probably serves to reduce the chronic irritation.[25] These bodies may be found in the sputum, lung, pleura, lymph nodes and spleen.[25] Their presence is held to be evidence of exposure to asbestos but by themselves are not necessarily an indication of asbestosis.[17,27,28]

The third and most significant tissue response is the production of fibroblasts and the deposition of collagen about the distal bronchioles and alveoli. There ensues a diffuse fibrosis which compresses the alveoli and capillaries, resulting in complete obliteration of the involved pulmonary tissue. This process is more pronounced in the lower lobes of the lung for it is there that the particles are most abundant. By x-ray one sees a fine, ground glass or granular pattern in the lower lobes and frequently emphysema in the upper lobes.

The sequence of pathologic events described previously occurs slowly. In man the fibrosis tends to progress even after the exposure has ceased; however in animals this does not seem to be the case. It may be that intercurrent infection contributes to the progression in man.[13]

In general there is a delay of five to seven years between the initial exposure to high concentrations of asbestos dusts and the onset of clinical asbestosis. The average interval reported by Merewether is eleven years.[17] While most patients with asbestosis have had an exposure of ten to sixteen years, it is important to realize that the disease has occurred with as short an industrial exposure as 0.5 years.[1,2]

Usually no symptoms appear until a large part of the respiratory reserve has been reduced by the fibrosis. Merewether has frequently commented how markedly the lungs can be affected and yet the patient be fairly comfortable.[17] However, when symptoms once begin and significant dyspnea becomes apparent, there is usually a definite and rapid progression. Then productive cough, anorexia, weight loss and fatigue are the common complaints. Death eventually results from intercurrent infection, cor pulmonale or carcinoma of the lung.

The case herein presented demonstrates many of the significant features in the pathogenesis, symptomatology and natural course of asbestosis. The patient had worked for twelve years in an atmosphere having a concentration of asbestos particles known to be sufficient to produce pulmonary pathology. However, it was only during the last year of life that dyspnea, cough, anorexia and weight loss manifested themselves. Clubbing had been present for at least five years. He had a very rapid downhill course, due undoubtedly to the two associated factors—the asbestosis and carcinoma of the lung. The physical findings of clubbing, cyanosis and dullness at the lung bases were all consistent with asbestosis as were the x-ray findings in the lungs, apart from the evidence suggesting neoplasm. The outstanding symptom, the severe and progressive dyspnea, was attributed to a combination of pulmonary fibrosis, superimposed and spreading lung neoplasm, pulmonary infection and finally congestive failure on the basis of cor pulmonale.

As indicated in the case history, the ten-day period of ACTH therapy was accompanied only by euphoria but objective measurements revealed no significant changes. This was not surprising for two reasons: (1) the fibrosis had obviously been of long duration and therefore one would not expect it to change much at this time; and (2) he had superimposed bronchogenic carcinoma. It is of interest to compare these results to patients with chronic beryllium

poisoning who usually show a favorable response to steroid therapy.[29]

Two further aspects of this case merit more detailed consideration and analysis: (1) the pulmonary function and cardiac catheterization studies; and (2) the significance of the superimposed bronchogenic carcinoma.

PULMONARY FUNCTION AND CARDIAC CATHETERIZATION STUDIES

Table I indicates, as one might expect, that the patient had a reduction in vital and maximum breathing capacities. However, the finding of an alveolar-arterial oxygen gradient of 27 mm. Hg demonstrates that one of the disturbances in pulmonary function was a defect in the diffusion of oxygen from the alveoli of the lungs to the capillaries. This corresponds to the syndrome of "alveolar-capillary block" described by Baldwin, Cournand and Richards[31,32] and again by Austrian et al.[33] This diffusion defect is not surprising when one recalls the fibrosis about the alveoli, alveolar ducts, capillaries and bronchioles that occurs in asbestosis. In order for the patient to maintain a near normal arterial oxygen saturation, a high alveolar oxygen was necessary; and this apparently was accomplished in part by hyperventilation. The patient had an average respiratory rate of 40 per minute at rest. This compensatory mechanism apparently was not adequate during stress or exercise for under those conditions the arterial oxygen saturation fell. There was a considerable degree of pulmonary hypertension and, as in the cases of pulmonary fibrosis studied by Cournand and his associates, a rise in the pulmonary artery pressure occurred with exercise. (Table II.) The partial pressure of carbon dioxide in the blood (36 mm. Hg) was low normal rather than elevated. Had there been a defect in alveolar ventilation, the pCO_2 would probably have been higher. As Arnot emphasized in discussing this case[16] carbon dioxide is not impaired in its transfer from the blood to the alveoli because of its great diffusion capacity. This speed of diffusion plus the increased alveolar ventilation no doubt accounted for the lowered pCO_2 value.

ASBESTOSIS AND CARCINOMA OF THE LUNG

The association of asbestosis and carcinoma of the lung has been mentioned frequently in the literature.[1–3,34–53] Heretofore some authors have believed that the cases were too few in number to be of significance; others, especially Vorwald and Karr, have stated that "inhaled dusts, except those containing recognized carcinogenic substances (as radium and tar) cannot in general be considered as etiologic factors in the development of primary pulmonary carcinoma."[4] Our conclusion at present is in favor of the concept that the association of bronchogenic carcinoma with asbestosis is more than coincidence. That there is a significant incidence of bronchogenic carcinoma in asbestosis is apparent from Table III.

TABLE III
INCIDENCE OF ASBESTOSIS AND CARCINOMA OF LUNG

Author	No. of Deaths with Asbestosis	No. Due to Cancer of Lung	Incidence (%)
Merewether[1]	235	31	13.2
Wedler[45]	92	15	16.3
Wyers[2]	115	17	14.8
Lynch, Cannon[47]	40	3	7.5
Gloyne[3]	121	17	14.1
Total	603	83	13.8

Merewether has cited the largest series—of 235 cases of asbestosis there were thirty-one with bronchogenic carcinoma, or 13.2 per cent.[1] An average of the five analyses recorded in the literature is 13.8 per cent. This is considerably higher than the incidence of lung carcinoma in routine necropsies, which in a comparable period (1935–1948) ranged from 0.8 to 2.4 per cent.[9,47,54]

In contrast to asbestosis the incidence of bronchogenic carcinoma in silicosis as recorded in the two largest series has been similar to what might be expected in the general population. The data compiled by Merewether[1] and the Miner's Phthisis Medical Bureau of South Africa[55] are based on a total of 6,884 and 1,438 autopsied cases of silicosis respectively, and disclose an incidence of lung carcinoma of 1.32 and 0.70 per cent. Vorwald and Karr found two lung carcinomas in 136 silicotics (1.47 per cent). Klotz[56] noted an incidence of 8 per cent, but his series of fifty cases does not seem large enough to be statistically significant. However Gloyne[3] in reviewing necropsy material from 1929 to 1949 (796 cases) also described the surprisingly high incidence of lung carcinoma in silicosis of 6.9 per cent, and 7.7 per cent in

the pneumoconioses as a whole. In this same series 8.3 per cent of cases without any pneumoconiosis had cancer of the lung. Merewether and Gloyne's cases were analyzed over a comparable period of time so that it seems unreasonable to interpret the figure of 6.9 per cent as reflecting the increase of lung carcinoma in the general population. The discrepancy in the data probably is explained by the fact that Gloyne's material was selected from the pneumoconioses in which the histories and x-rays were "unusual."

Gloyne noted that 14.1 per cent of patients with asbestosis had lung carcinoma. This figure parallels the observations of previous workers and is significantly above that recorded for silicosis. As has been mentioned the asbestos particle probably acts as a mechanical irritant while the pulmonary changes in silicosis are considered due to the chemical properties of silica.[18,20]

Carcinoma of the lung appears to be prominent in females with asbestosis. Of Merewether's thirty-one cases nine were females, or 29 per cent, and in Gloyne's series of seventeen cases the incidence was 41 per cent. In the published autopsy reports data as to the sex of the patient are available in twenty-three, of which five (21 per cent) were females. In contrast, the incidence of bronchogenic carcinoma in females in the general population is considerably lower. Lindskog noted an incidence of 4.0 per cent,[57] Graham[7] 5.4 per cent, Doll and Hill[8] 8.4 per cent and Ochsner[10] 10.3 per cent. The higher figure in asbestosis supports the theory that asbestos particles act as carcinogens.

Experimental production of neoplasms has demonstrated that chronic irritation of body tissues by mechanical means may predispose to the development of malignancy. Asbestos particles when lodged in the finer bronchioles serve as mechanical irritants to the bronchial epithelium. The squamous metaplasia of the lungs found frequently in asbestosis is presumably a consequence of prolonged irritation in the lower respiratory tract. Some pathologists consider squamous metaplasia as an alteration in the cellular structure that may precede or be the initial step towards the development of squamous cell carcinoma.[58]

A "lag period" between the exposure to a possible carcinogen and the onset of malignancy is characteristic. Nordmann[38] noted in his cases that the average duration between the initial exposure to asbestos and the development of bronchogenic carcinoma was about eighteen years. Similarly Merewether[1] found that patients dying of carcinoma of the lung had a longer mean exposure to asbestos (16.5 years) than those dying with no evidence of malignancy (13.4 years). Finally, a short but "adequate" exposure may be followed by pulmonary malignancy many years later. In Merewether's series is the case of a woman who was an asbestos worker for only six months yet later developed lung carcinoma. Gloyne[35] reported the case of a woman with an exposure of nineteen months who died fifteen years later at the age of seventy-one with a squamous cell carcinoma of the right lower lobe.

Table IV summarizes the pertinent information of the twenty cases of asbestosis with lung carcinoma that have been autopsied and recorded in the available literature. Four cases have been added to the list compiled by Homburger[46] in 1943. It is noted that in about four-fifths of the cases in which the primary site is indicated the origin of the neoplasms was in the lower lobes. This is in contrast to the general population where bronchogenic carcinoma seems to be more frequent in the upper lobes. In Lindskog's[59] series there was an incidence of 57 per cent in the upper lobes, 26 per cent in the lower lobes. Ochsner[10] found 56 per cent in the upper lobes and 35 per cent in the lower lobes. No conclusions should be drawn from the small number of cases listed in Table IV. Nevertheless, since asbestos particles lodge to a greater extent in the lower respiratory tree where the changes of asbestosis are also more pronounced, a higher incidence of carcinoma in this location should be expected if an etiologic relationship exists. In our case the asbestosis was widespread and severe, and the tumor, which originated in the inferior (lingual) segment of the left upper lobe, was in an area significantly involved by the fibrosis and inflammation of asbestosis.

It is also noted in Table IV that twelve of the nineteen previously recorded cases had lesions of the squamous cell type. The incidence of squamous cell carcinoma is said to be high in male cigarette smokers with pulmonary malignancy.[6] At autopsy our patient showed both squamous metaplasia and adenocarcinoma of the lingula. It may be of significance that he was a chain smoker for over twenty years in view of the observation by Wynder and Graham[7] that males with adenocarcinoma of the lung are

frequently chain smokers. However, it is our belief that the presence of an adenocarcinoma rather than one of the squamous cell type may be explained by the fact that it is not unusual to find several cellular types in various sections of the same tumor.[58] Therefore morphologic differences in cell arrangements may not really represent different etiologic varieties of cancer.

TABLE IV

SUMMARY OF PUBLISHED CASE REPORTS IN WHICH AUTOPSY DATA ARE CITED

Authors	Year	Sex and Age	Occupation	Duration of Exposure (yr.)	Freedom from Exposure before Death	Nature of Tumor	Primary Site	Metastases
Lynch, Smith[34]	1935	M, 57	Weaver	21	4 mo.	Squamous cell	R.L.L.	Many nodules in R.L.L.
Gloyne[35]	1935	F, 35	Spinner	8	9 yr.	Squamous cell	R.U.L.	Pleura
Gloyne	1935	F, 71	Mattress and opening departments	1½	15 yr.	Squamous cell	R.L.L.	None
Egbert, Geiger[37]	1936	M, 41	Weaver	17	2 yr.	Glandular	L.L.L.	Widespread
Gloyne[38]	1936	M, 59	Packer, stores department	10½	? mo.	Oat cell	L.L.L.	L.U.L. and pleura
Nordmann[38]	1938	F, 35	Carder, spinner, weaver	7	9 yr.	Squamous cell	L.L.L.	Liver, kidneys
Nordmann	1938	M, 55	Prespinning assembly room	7	12 yr.	Squamous cell	L.L.L.	Widespread
Lynch,[39] Smith	1939	M, 50	Weaver	13	3 yr.	Squamous with glandular features	R.L.L.	Pleura, mediastinal nodes
Holleb,[44] Angrist	1941	M, 52	Pipe insulator	25	9 yr.	Non-keratinizing squamous celled	R.U.L.	Mediastinal nodes, adrenal, kidney
Holleb, Angrist	1941	M, 50	Pipe insulator	25	10 yr.	Oat cell	R.L.L.	Widespread, including brain
Linzbach, Wedler[41]	1941	M, 61		> 3	Not known	Squamous cell	R.L.L.	None
Desmeules et al.[48]	1941	M, 57	Machine adjustor	25	1 mo.	Alveolar cell	L. lung	Pleura
Desmeules et al	1941	M, 50	Bagger	22	4 mo.	Squamous cell	R. lung	Pleura
Homburger[46]	1942	M, 45	Not known	5	1 yr.	Squamous cell	R. lung	Diaphragm
Homburger	1942	M, 43	Not known	20	17 mo.	Anaplastic	L.L.L.	Pleura
Homburger	1942	F, 49	No known contact with asbestos	Not known		Squamous cell	R. lung	Liver, adrenal, stomach, hilar lymph nodes
Cureton[49]	1948	F, 37	Pipe coverer	7	15 yr.	Squamous cell	L.L.L.	Pericardium, liver, kidney, ovaries, femur
Owen[51]	1951	M, 39	Asbestos worker	1	20 yr.	Adenocarcinoma	R. lung	None
Stoll, Bass, Angrist[52]	1951	M, 40	Pipe coverer	6	About 4 to 5 yr.	Anaplastic	No definite site	Kidneys, brain, liver
Present authors	1952	M, 41	Asbestos mill worker; sorter	12	2 yr.	Adenocarcinoma	Lingula	Myocardium, pericardium, spine, regional nodes

SUMMARY AND CONCLUSIONS

1. A case of asbestosis with superimposed adenocarcinoma of the lung with metastases, following documented harmful industrial exposure, is presented.

2. ACTH (adrenocorticotrophic hormone) was given with no objective changes in the patient's clinical course.

3. Pulmonary function and cardiac catheterization studies were performed before and after ACTH. They revealed an alveolar diffusion defect and pulmonary hypertension.

4. Asbestos is associated with bronchogenic carcinoma in 13.8 per cent of the cases cited in the literature. In silicosis the incidence is considerably less than this. The asbestos particle may serve as a carcinogen because of the chronic mechanical irritation it produces.

5. Since there are approximately 10,000 workers engaged in potentially hazardous asbestos operations in this country, it is reasonable to assume that there are many unrecognized cases of asbestosis. From the evidence presented a higher incidence of bronchogenic carcinoma should be expected in this group.

Addendum: Since the submission of this manuscript a similar case has been observed by us (MGH #778205). The patient was a forty-six year old contractor's helper whose work since age seventeen consisted of cutting and sawing asbestos board to insulate pipes, boilers and refrigerators. For years he had smoked one package of cigarettes daily. He died after a year of illness during the last four months of which he received 5,000 r of deep x-ray to the left chest.

At autopsy the lungs were firm and weighed 3,350 gm. There was a poorly differentiated adenocarcinoma arising from the left lower lobe bronchus, almost completely replacing the left lower lobe. The tumor had spread to the left upper lobe, hilum, pericardium, pleura and diaphragm; and had metastasized to the right lung and adrenal. The remaining lung tissue showed peribronchial fibrosis, focal alveolar wall thickening and numerous asbestosis bodies, surrounded by macrophages filled with asbestosis body particles and foreign body giant cells. The asbestosis bodies were seen in equal distribution in all parts of the lungs not completely involved by tumor.

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Acute Diffuse Pulmonary Granulomatosis in Bridge Workers*

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In the past decade sporadic reports have appeared of a newly identified clinical entity which has variously been called: primary atypical pneumonia,[1] epidemic pulmonary disease,[2] cave sickness,[3] diffuse miliary granulomatous pneumonitis,[4,5] acute miliary pneumonitis,[6,7] and an unusual pulmonary disease.[8,9] It occurs with a high attack rate in groups exposed in an unusual situation, varying somewhat from one report to another but generally associated with finely divided organic matter. The exposures have included dust from abandoned homes, barns and chicken-coops in Missouri;[1] dust from a new road in Oklahoma;[8] dust in an abandoned chalk mine in Arkansas;[3,10] dust from dead pigeons and their excreta in an old church in Plattsburg, New York;[6,7] dead pigeons and damp excreta in an old water tower in Cincinnati, Ohio;[4] and mere presence in an abandoned storm cellar in Oklahoma, said not to be notably damp or dusty.[8]

This syndrome has been characterized by grippe-like symptoms with few physical findings, a diffuse lobular pneumonic roentgenologic appearance, and negative chemical, cultural and serologic diagnostic studies. The onset may be stormy but the course is usually mild and protracted. Full recovery ensues after several months in some cases, while there is mild persistent fatigue, exertional dyspnea, cough or chest pain in others. The roentgenographic infiltrate either clears slowly or, more commonly, remains as a fine nodular residuum after initial clearing. In all but one group calcification occurred in varying percentages, eight months to several years after the onset of symptoms.[7,11]

The etiology of this entity has not been definitely established. Indeed, the inability to find an etiologic agent after thorough study is one of the many features common to the reported cases. Pathologic studies have been made in only one patient, who died during convalescence from an unrelated illness. Scattered non-specific granulomatous lesions with a caseous type of central necrosis were present in both lungs. No tubercle bacilli or other organisms were found.[4]

We have recently had occasion to observe a small outbreak of this syndrome in relation to still another type of dust exposure. It is the purpose of this paper to present these cases and briefly to survey the pertinent literature.

CASE REPORTS

CASE I. H. L., a sixty-two year old Greek construction painter, was admitted to the Chest Service of Bellevue Hospital on August 23, 1951, complaining of weakness and weight loss.

The patient had left New York City in late June, 1951, to work with a crew painting highway bridges in the rural region south of Baltimore, Maryland. He and one other man (Case II) spent a large part of their working time in scraping these bridges prior to painting. No other member of the crew (with the occasional exception of the foreman) assisted in this part of the operation. While this foreman developed grippe-like symptoms at the time both patients became ill, he did not consult a physician and has been unavailable for study by the authors.

Over the period of one month the steel understructures of three bridges on concrete pilings were scraped free of an estimated 0.5 to 3 inch crust of dried mud, débris and bird or bat droppings. Two bridges were in Anne Arundel County, the first spanning a small river near Baltimore and the other, railroad tracks near Odenton. The third bridge, which crossed an abandoned railroad culvert, was located near

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Paris in Calvert County. The job was done by hand, using steel brushes, and exposed the two men to a heavy cloud of dust. Bird-like creatures were found in the dark holes formed by the steel and concrete components of the understructure of the last bridge and had to be forcibly evicted. These creatures were said to be bats by local residents and the patients tended to confirm this identification by description and reference to nature photographs. They estimated that approximately one-third of the crust on this bridge was composed of the excreta of these animals. As recalled by the patients four months later work proceeded simultaneously on all three bridges rather than to completion on one at a time. It is therefore not possible to single out one location as the probable site of infection.

Four weeks before admission to the hospital (and four weeks after starting work in Maryland) the patient sustained minor trauma to the thorax, which was followed by vague nonpleuritic aching of the left anterior chest. The next day he was exposed to a heavy downpour of rain and that same evening developed shaking chills, malaise, fever, sweating, anorexia, headache, muscular aches and a mild cough with scant mucoid sputum. A physician who had advised use of local heat to the thorax the day before then prescribed oral penicillin which the patient took for one week. During this period the acute syndrome abated gradually, and he returned to New York City with persistent malaise, weakness, anorexia and scant cough. These symptoms also gradually improved over the next two weeks but he continued to lose weight and consulted another physician a few days before entry to the hospital. He was referred to the New York City Department of Health which, after a chest roentgenogram was taken, sent him to the Chest Service of Bellevue Hospital.

The patient was born in Greece and had travelled around the world as a seaman before he came to this country in 1924, at the age of thirty-five. He had since worked as a house and construction painter and had never been outside the confines of New York, New Jersey and Pennsylvania until the present episode. He had never done any sandblasting or at any time been exposed to silica or other occupational dusts. His health had been excellent, except for malaria and gonorrhea in his youth, and two bouts of pneumonia without sequelae in 1922 and 1928. In the past year occasional nocturia had been noted, without other genitourinary symptoms.

Physical examination revealed a small man who appeared chronically ill. The temperature was 100°F., the pulse 84, respirations 18, blood pressure 120 systolic and 70 diastolic.

The head and neck were normal. The tonsils were atrophic, and there were no oropharyngeal lesions. A few small, soft axillary lymph nodes were palpable but there was no generalized glandular enlargement. The structure and respiratory excursions of the thorax were normal. Examination of the lungs revealed moderate hyper-resonance throughout, with slight diminution of the breath sounds posteriorly and slight harshness anteriorly; there were no rales, rhonchi or wheezes. A soft blowing systolic murmur was heard at the cardiac apex but there were no other abnormal cardiac findings. The prostate was firm, smooth and slightly enlarged. Small, bilateral, easily reducible indirect inguinal hernias were present. The abdomen, extremities and skin were normal. There was no hepatosplenomegaly.

The initial chest roentgenogram revealed diffuse sprinkling of both lungs by 0.5 to 3 mm. dense, fuzzy, round and oval shadows with occasional coalescence, interconnection and circular grouping; the concentration of these in the apical thirds of the lungs was less marked than elsewhere. There was some enlargement of the right root shadow. (Fig. 1.)

The hemoglobin was 14 gm./100 cc. and white cell count 10,400. After one week the latter fell to 8,000 and remained close to that level during the rest of his hospitalization. The differential count was normal except for eosinophilia of 4 per cent on one occasion. The erythrocyte sedimentation rate varied from 75 to 45 mm./hr. (Westergren). The stools were persistently negative for occult blood.

Gram and methylene blue stains of the sputum revealed polymorphonuclear leukocytes and mononuclear cells, with the usual bacterial flora. No fungi were seen. Two sputum cultures on blood agar were negative for pathogenic bacteria after one month's incubation at 37°c. Five sputum smears, three sputum cultures, six gastric cultures, three twenty-four-hour urine cultures, one spinal fluid culture and one bone marrow culture were negative for acid-fast bacilli. On Sabouraud's medium one sputum culture grew a torula which was considered

by the mycologist* to be non-pathogenic; four gastric cultures, two additional sputum cultures, two bone marrow cultures, and one twenty-four-hour urine culture for fungi showed no growth at 37°C. or at room temperature.

The tuberculin patch test and first (0.00002 mg.) and second (0.005 mg.) strength intradermal tests with P.P.D. were negative, as were blastomycin and coccidioidin skin tests. Intradermal histoplasmin,®† using 0.1 cc. of 1:1000-dilution, produced a 1 cm. area of induration and erythema. Cold agglutinin, heterophile antibody, brucella, syphilis, Weil-Felix, Q fever, ornithosis-psittacosis, typhoid and paratyphoid fever serologic tests were negative. A complement-fixation test for histoplasmosis, fifty-three days after onset of the patient's illness, was reported positive undiluted; another, seven and one-half months after onset, positive 1:64; and a third, nine months after onset, positive 1:4.‡

The icterus index, total serum protein, serum albumin, serum globulin, cephalin-cholesterol flocculation, alkaline and acid phosphatase, inorganic phosphorus and blood urea nitrogen were normal. Roentgenologic studies of the stomach and duodenum, small intestine and colon, and osseous system—including hands, feet and skull—were normal. Intravenous and retrograde pyelograms showed normal structure and function of the urinary tract. Cystoscopy disclosed no abnormality. Bronchoscopy, performed one month after the beginning of the patient's illness, showed only some diffuse reddening and edema of the bronchial mucosa. The only abnormalities in the electrocardiogram were slight splintering of the QRS complexes in the standard and limb leads, and an Rsr′ pattern in V_2 and V_3. There was left deviation of the electrical axis with horizontal electrical position of the heart, sinus rhythm and a rare premature auricular contraction. No changes were noted on several tracings and there was nothing in the clinical picture to warrant a diagnosis of right ventricular enlargement.

Biopsy of a lymph node from the right axilla revealed chronic lymphadenitis, and the morphology of aspirated bone marrow was normal. No fungi were seen in either specimen and there were no intracellular organisms.

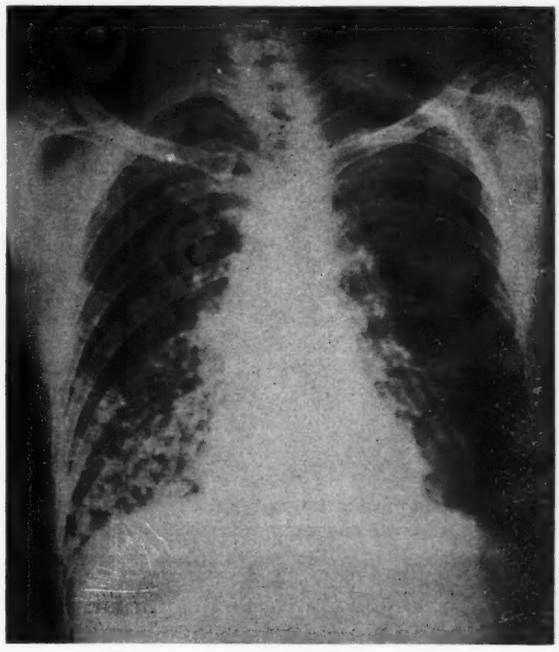

FIG. 1. Chest roentgenogram of Case 1, H. L., one month after onset of symptoms.

Since no etiologic agent could be found, the patient received no specific therapy but was kept at rest in the hospital for three months. There was little change in his clinical condition until the second week when the temperature fell to normal levels. His symptoms began to clear and a sense of well being was noted at this time. The mild cough persisted, however, and he continued to raise 10 to 15 cc. of clear mucoid sputum, containing a few flecks of greenish material, each day. He started gaining weight and added 20 pounds by the time of discharge. Although coarse moist rales were heard at the posterior lung bases in the third hospital week, they gradually disappeared over the course of a month, and there were no other changes in the physical examination throughout his hospital stay. No hepatosplenomegaly or lesions of the skin, mucosae or tonsils were ever found.

The appearance of the chest roentgenograms did not change during the patient's first month in the hospital. Then began a very slow and slightly irregular process of clearing, with gradual shrinkage in the size of the individual shadows. The most striking change was in the upper half of the left lung. (Fig. 2.)

* Dr. Frederick Reiss, Director, and Miss Leona Caroline, Technician, The Dermatological Research Laboratory, New York University-Bellevue Medical Center, New York, N. Y.

† A product of Eli Lilly.

‡ The histoplasmosis complement-fixation tests were performed by The Mycology Laboratory, Communicable Disease Center, United States Public Health Service, Chamblee, Ga.

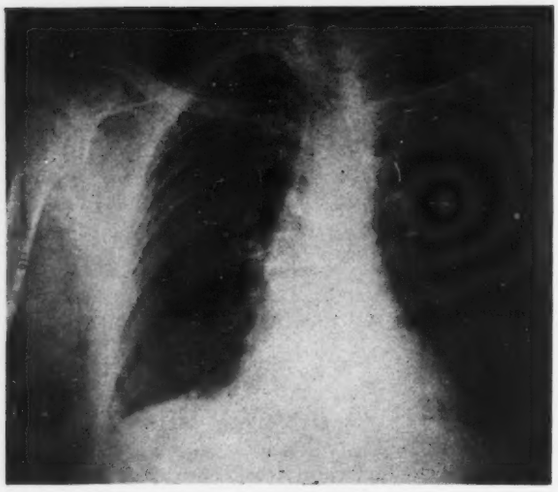

FIG. 2. Chest roentgenogram of Case I, H. L., six months after onset of symptoms.

The progressive clinical and roentgenologic improvement and the results of the diagnostic work-up ruled out many possibilities but did not establish an etiologic diagnosis. The patient was discharged in November, 1951, to be followed in the Chest Clinic at monthly intervals.

At the time of his latest clinic visit in November, 1952, fifteen months after the onset of his illness, the patient was still totally asymptomatic except for occasional non-productive cough. His latest films have shown continuance of the gradual clearing. This process is more than half complete, and there is, so far, no evidence of calcification.

CASE II.* J. V., a forty-seven year old Greek construction painter and fellow-worker of H. L., was admitted to another hospital on August 14, 1951, complaining of cough, dyspnea and weakness.

The patient had been in good health, working at the same job and for the same period of time as H. L. Four days after H. L. became ill the patient developed shaking chills, fever, dyspnea, cough and weakness and returned to New York City. One day before admission to the hospital he received oral aureomycin and one injection of penicillin, without effect on his symptoms.

This patient's past and geographic history was similar in all respects to that of H. L. except that for two weeks in 1950 he had been exposed to the dust of sandblasting. He had had pneumonia in 1924 and had, in recent years, noticed postprandial indigestion and fatty food intolerance.

* Case II is reported through the courtesy of the patient's physician, Dr. George S. Vamvas of Brooklyn, N. Y.

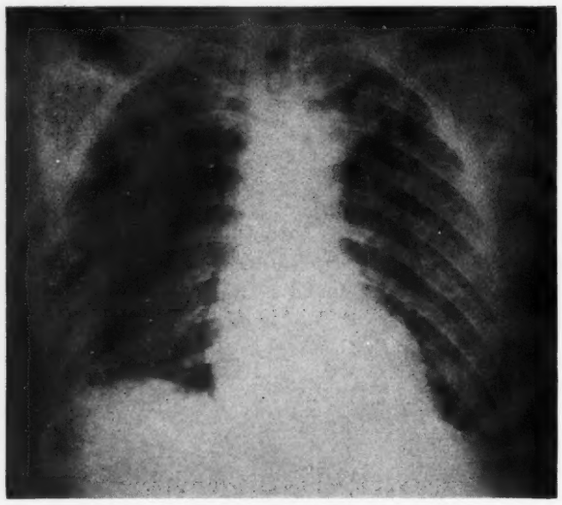

FIG. 3. Chest roentgenogram of Case II, J. V., three weeks after onset of symptoms.

Physical examination disclosed an underweight, acutely ill man who was dyspneic out of proportion to the physical findings. The temperature was 103°F. The throat was clear. Subcrepitant rales were heard at both lung bases but there were no signs of consolidation. The heart was not enlarged and no murmurs were heard. The abdomen was soft and the liver and spleen were not felt.

The initial chest roentgenogram showed a striking and diffuse infiltration with fuzzy, match-head sized densities, similar to but larger and more numerous than those of H. L. (Fig. 3.) Sputum and gastric cultures for acid-fast bacilli were negative, as was a blood culture for pathogenic bacteria. Tuberculin patch and intradermal tests with P.P.D. were negative.

In the hospital the patient continued his previous symptomatology and ran a spiking fever, despite aureomycin and dihydrostreptomycin, until the tenth day. Thereafter he improved progressively until the time of discharge although slight cough and mild exertional dyspnea persisted. Chest roentgenograms showed some increase in the size of the individual shadows during the second hospital week but these began to shrink after the third week. Because of the progressive improvement the patient was discharged, at his own request, on the twenty-fourth hospital day.

This patient was feeling well when last seen, in October and November, 1951, except for mild exertional dyspnea and easy fatigability. The roentgenologic appearance of his lungs had continued to clear slowly and there was no

calcification. (Fig. 4.) At this time an intradermal histoplasmin skin test was positive in 1:1000 dilution, ornithosis-psittacosis serology was negative, and a histoplasmin complement-fixation test was positive in 1:2 dilution.

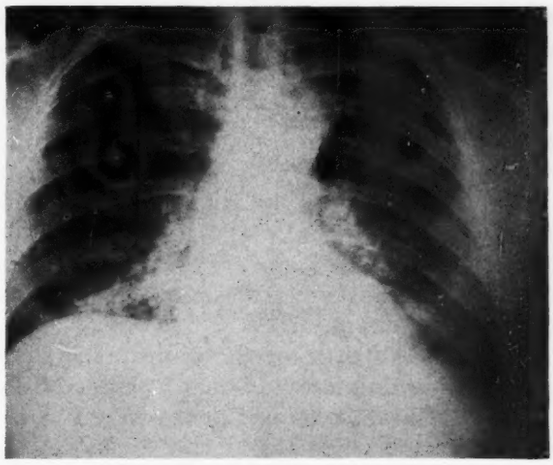

FIG. 4. Chest roentgenogram of Case II, J. V., three months after onset of symptoms.

COMMENTS

The syndrome exhibited by these two patients seems to resemble closely that of acute diffuse pulmonary granulomatosis as described earlier. It should be emphasized, however, that the diagnosis is based upon the striking and surprisingly specific clinical picture occurring in a localized outbreak. In an isolated case a large variety of inhalatory or contact diseases of infectious, toxic or allergic origin is superficially suggested. Thirty-two different conditions, according to the studies of Felson and Heublein, may cause a similar roentgen appearance in any single case.[12] Nevertheless, considerations such as clinical onset and course of the illness eliminate some of these possibilities, while careful laboratory investigations eliminate many more in this and the other reports.

The present cases introduce a hitherto unreported type of exposure, namely, the dust arising from bridge scraping in rural Maryland, and possibly implicate the excreta of bats. The last has not been mentioned in previous reports but it is of considerable interest in view of exposure to other animal forms in some reports and to abandoned or confined places in all. Cave dust frequently contains bat guano which, when inhaled in high concentrations, is said to cause shortness of breath and inspiratory chest pain for a few days.[10]

Of all the etiologic possibilities in the various studies of this syndrome only histoplasmosis has received any significant support. White and Hill, in a thorough recent study, conclude that acute diffuse pulmonary granulomatosis, and also multiple pulmonary calcifications in normal individuals, result from the inhalation of dust containing Histoplasma capsulatum or an antigenically related organism. They did not isolate the organism but did find positive skin tests and complement fixations and eventual multiple pulmonary calcifications in a high percentage of the cases in the Plattsburg epidemic of "acute miliary pneumonia" which followed exposure to pigeon manure. Further, in a group of 114 healthy residents of rural upper New York State, with multiple pulmonary calcifications, 95 per cent had been exposed to dust in relation to pigeons, fowl or threshing; 94 per cent reacted to histoplasmin, 52 per cent reacted to tuberculin; and, in the entire group the only fifteen individuals with chronic respiratory symptoms could relate the onset thereof to an organic dust exposure.[7]

Further support for the concept that this syndrome results from inhalation of dust containing H. capsulatum is supplied by four different types of indirect evidence. First, groups of cases from most of the reported outbreaks have been restudied and found to have developed positive skin or complement fixation reactions in varying percentages.[7,11,13] The fact that these were negative at the time of the original studies may be explained by the well known depression of skin sensitivity during any form of critical illness,[14] and by the unsatisfactory nature of these testing materials in the early part of the past decade. In our cases the histoplasmin response was not studied until late in the course of the illness. Second, clinical pictures quite similar to that of acute diffuse pulmonary granulomatosis have been seen in proven cases of histoplasmosis in which dust is not specifically mentioned.[15–17] The possibility remains that minor dust exposures did play a role but were not recalled in the patients' histories. Third, at least one earlier case of proven histoplasmosis has definitely followed heavy dust inhalation.[15] Fourth, dust has been implicated as the vehicle of infection in other fungus diseases. Coccidiomycosis, which is so similar to histoplasmosis in many respects, is the most striking example.[18] Furthermore, isolated reports have appeared in which dust-borne

fungus infection has been suspected in Parisian squab-feeders, French wigmakers,[19] Ceylon tea-tasters,[20] agricultural[21,22] and bagasse workers,[23] and others.[24–26] In this regard, it is perhaps noteworthy that some of the cases of pneumonia epidemic in the early years of the mid-western "Dust Bowl" storms had clinical and roentgenologic pictures similar to that of acute diffuse pulmonary granulomatosis. Study of dust in the area at that time, however, revealed no causative organism.[27,28]

Three particularly cogent arguments in favor of an inhaled fungus origin of acute diffuse pulmonary granulomatosis have recently come to our attention. Grayston, Loosli and Alexander[29] have reported three cases of a similar clinical and roentgenologic nature due to inhaling dust from a long-unused silo in Indiana. Histoplasmin skin and complement fixation reactions were positive, and the organism was recovered both from the dust in the silo and from the sputum of the one case available for study. These patients have been followed and the pulmonary infiltrates are now undergoing calcification.[30] Schwarz[31] has also cultured this organism in studying soil from the water tower where the Cincinnati outbreak of "diffuse miliary granulomatous pneumonitis" had its origin. Finally, Furcolow, who has investigated the epidemiology of the known outbreaks, has recovered the organism from the soil of the abandoned storm cellar implicated in one of the Oklahoma epidemics,[32] and from soil at the point source of eleven others.[11] The eleven include all of the reports previously mentioned (with the exception of the Plattsburg cases) and four heretofore unreported outbreaks.[11,33] This work furnishes the most conclusive evidence to date that H. capsulatum is the cause of this syndrome via dust inhalation.

It is not within the scope of this paper to review the voluminous literature on histoplasmosis; this has been done well in many recent publications.[7,34–37] It does seem pertinent, though, to present certain features for correlation with the earlier part of this discussion. Histoplasmosis was once considered a rare, fatal and always disseminated disease and has been reported from various parts of the world. The demonstration that diffuse pulmonary calcifications in healthy individuals are most common in the Central and East Central United States, and that these bear a positive correlation with histoplasmin rather than with tuberculin sensitivity, suggest that histoplasmosis may be a widespread, usually mild disease in this endemic region. In recent years, moreover, increasing numbers of culturally proven, non-fatal cases of both localized and disseminated types have been reported. The clinical aspects and roentgenologic appearance of histoplasmosis may vary widely from case to case but most commonly simulate atypical pneumonia or the various forms of tuberculosis. Indolent pulmonary lesions have been noted to undergo calcification over a period of years. Although the route of infection has not been established, respiratory inoculation has been generally accepted for the majority of cases. In addition, air-borne infection is considered quite likely in view of the recent isolation of H. capsulatum from humus-containing soil and a variety of animals in the endemic area.[38]

The use of skin and serologic tests as diagnostic tools in surveys of pulmonary calcification and in individual cases of histoplasmosis has not met with universal approval. Cross reactions with blastomycin, coccidioidin and haplosporangin may occur.[39] There is considerable controversy as to whether or not there is a stronger reaction to the specific antigen than to those which give cross reactions.[40,41] Skin sensitivity seems to have the same significance as in tuberculosis, but complement-fixation titers may fall rapidly within a few weeks after initial infection.[42] Caution must therefore be exercised in interpreting both positive and negative tests in the individual diagnostic problem.

The similarities between the reported cases of proven and probable histoplasmosis and those of the syndrome of acute diffuse pulmonary granulomatosis have been quoted. Certain dissimilar features, however, require further consideration. The clinical picture of histoplasmosis may vary widely, while that of acute diffuse pulmonary granulomatosis is quite uniform. The pulmonary lesion in histoplasmosis may also vary but a diffuse, finely nodular type of infiltrate has been noted in all cases of acute diffuse pulmonary granulomatosis. Finally, small outbreaks following exposure to finely divided organic matter have not been reported frequently in histoplasmosis but have been a prominent feature in acute diffuse pulmonary granulomatosis. Although these dissimilarities may mean that H. capsulatum does not cause this syndrome, the evidence to the contrary is

rapidly accumulating. No experimental proof can be cited but it would seem possible that the mode of infection could alter the clinical features of the disease. Factors which may play a role in producing a given type of clinical picture are presence, type, concentration and particle size of dust; number of organisms; or perhaps even modification of tissue reaction by inherent qualities of the inhaled dust itself. Further clinical and experimental work is required for clarification of the many unknown facets of this disease.

SUMMARY

Two cases of acute diffuse pulmonary granulomatosis are reported. A causative organism was not recovered. Inhalation of dust, which was raised by bridge scraping in rural Maryland and which may have contained bat guano, is considered responsible for the illness.

The syndrome of acute diffuse pulmonary granulomatosis and its etiology are reviewed briefly.

Inhalation of finely divided organic matter containing Histoplasma capsulatum is suggested as the probable cause of this syndrome.

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Ileojejunitis Involving the Entire Small Bowel

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Pathologic involvement in ileojejunitis is usually confined to the distal jejunum and the proximal ileum.[1] The disease is rarely so extensive as to involve the entire small bowel. We have recently seen two patients* in whom the x-rays revealed pathologic disorder extending from the ligament of Treitz to the ileocecal valve. This was confirmed by autopsy in one of the cases.

Despite complete and severe involvement of the small bowel one patient lived ten years and the other, with an eleven-year history, is still alive although there is marked evidence of nutritional edema. Diarrhea was a chief complaint but never very distressing. Loss of weight in both patients was marked, 30 to 60 pounds. Fever developed late in the course of the illness. The first case is also unusual because death by exsanguination has never been previously reported in this disease. The second case, in addition, reveals roentgen evidences of numerous intestinal fistulas. It is remarkable that with such extensive small bowel disease the digestive and absorptive capacity of the small bowel was apparently adequate for many years in the first case. The second patient, although presenting marked edema for seven years, has been carried along, albeit with frequent courses of supportive therapy. Undoubtedly, multiple short circuitings of the small bowel by entero-intestinal fistulas further reduced the surface area for absorption of nutrient elements and contributed to the development of edema and, in later stages, to generalized anasarca.

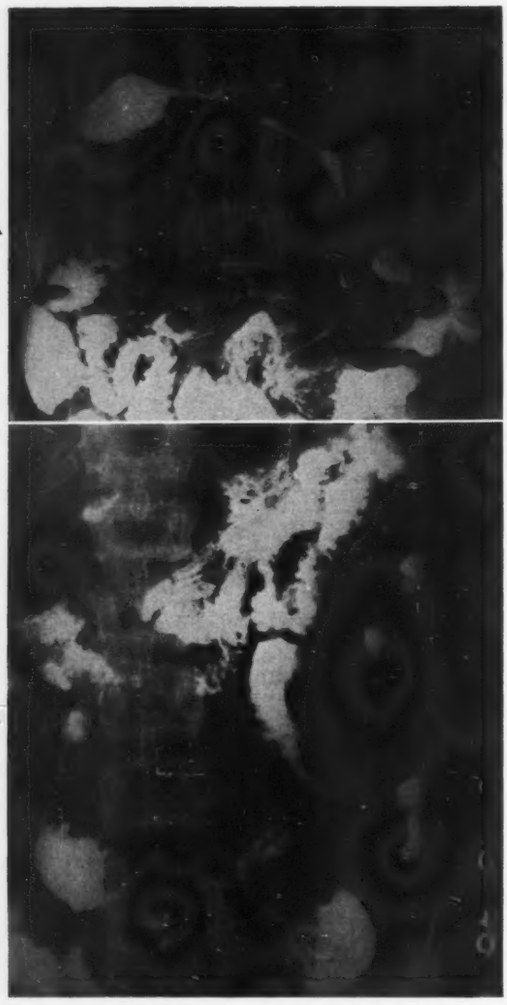
CASE REPORTS

Case 1. B. P., aged thirty, was admitted to the hospital in March, 1946, with a chief complaint of diarrhea and loss of weight. His present illness began five and a half years previously when he noticed gradually increasing constipation associated with rectal bleeding of bright red blood. One month later this was succeeded by a diarrhea of loose watery stools, numbering ten a day. In a six-month period the patient lost sixty pounds, his weight then being 140 pounds. In 1941 he was diagnosed as having ulcerative colitis. During the next three years the diarrhea subsided and he regained much of his weight. In November, 1944, he suffered a period of extreme emotional and physical distress; the diarrhea became worse and he was advised to go to Arizona. A transcript from a hospital admission in 1944 included the following positive data: malnourishment; edema of the rectal mucosa; hemoglobin 13.2 gm. per cent; red blood count 4,900,000 and white blood count 5,400 with a normal differential white count; negative x-ray of the chest. Serial films of the small bowel indicated an abnormal pattern with many areas of dilatation and constriction; an abnormal mucosal pattern was also noted in the colon. The diagnosis was regional ileitis and ulcerative colitis. He was treated with bed rest and radiotherapy and after one month of hospitalization was discharged still having three loose stools a day but without blood or pus in the fecal discharge. During the early part of 1945 symptoms were less annoying but toward the end of that year the attacks became more frequent and more disabling. A barium enema in September, 1945, was reported as showing "spastic colitis."

There had been no demonstrable fever at any time, although vomiting was occasional, abdominal cramps were frequent and a sense of bloating following meals was a common occurrence. There were never any joint pains. Conjunctivitis was severe whenever the diarrhea flared up but corneal lesions were absent. Stool frequency varied between two and five movements per day without blood.

Past history revealed tonsillectomy at fourteen years of age. In 1939, six months prior to the present illness, the patient fell a distance of 12 feet, lacerated his scalp and contused his back. He was not unconscious but was confined to bed for one week.

* From the private files of Dr. B. B. Crohn.



1A

1B

FIG. 1. A, widely separated loops of bowel surround masses formed by indurated mesentery. Long stenotic segments of bowel, resembling rigid pipe-stems, alternate with several small areas of dilatation. Diagnosis: Granulomatous ileojejunitis in the stenotic phase. B, the loops of bowel are markedly separated. Multiple areas of constriction alternate with areas of dilatation. The mucosa in the stenotic segments has a reticulated appearance. The entire small bowel appears to be involved.

Family history revealed that his father died of pulmonary tuberculosis in 1944 but the parent was not living at home.

Physical examination disclosed a poorly nourished white man, whose weight and height were 139 pounds and 5 feet 9 inches, respectively. The eyes revealed a moderate phlyctenular conjunctivitis; the tongue was smooth. The abdomen was the site of diffuse tenderness and the edge of the spleen was palpable. Rectal examination was negative and sigmoidoscopy disclosed a normal mucosa. Hematologic examination showed a hemoglobin of 11 gm. per cent, red blood count 3.2 million, white blood count 8,800 with 66 per cent neutrophils, 27 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophils. Stool guaiac was one plus.

A small bowel study revealed diffuse involvement of the entire jejunum and ileum by a chronic, granulomatous, inflammatory process with alternate dilated and constricted areas. The normal mucous membrane pattern was absent. "Cobblestoneing" was present in many segments. At the end of three and a half hours multiple "string signs" were evident. At the end of six hours more than half of the barium remained in the ileum. The cecum appeared deformed and the colon was abnormal. The diagnosis was diffuse ileojejunitis of the stenotic type, extending from the duodenum to the ileocecal valve with associated colitis. (Fig. 1.)

Fever first developed during this hospital stay. One month after admission the patient was discharged afebrile but with only symptomatic improvement. In June of that year fever recurred, as did the diarrhea, and for the first time he complained of right lower quadrant pain radiating through to the back. He was given liver extract, intramuscularly, vitamin B complex and sulfathalidine. Intermittent attacks of diarrhea, fever and pain occurred until April, 1947, but his weight climbed to 169, a gain of 30 pounds. At this time the hemoglobin was 14 gm. per cent. Stool frequency was two to five a day, with occasional bright red blood. The abdomen remained negative. X-ray films obtained in May, 1947, disclosed a dilated jejunum with distortion of the mucosal pattern. The ileum revealed little change from the previous study, with areas of constriction and dilatation and small, polypoid filling defects measuring 1–4 mm. in many of the loops.

In June, 1947, the patient was re-admitted to the Mt. Sinai Hospital because of diarrhea and abdominal pains. During a period of less than two weeks he had lost 20 pounds. Physical examination disclosed more evidence of weight loss. The heart and lungs were negative. The abdomen was sensitive throughout but no masses could be felt. The spleen was felt one fingerbreadth below the costal edge but was not tender, and the liver was barely palpable. Rectal examination, including sigmoidoscopy, was negative. Blood studies revealed no significant changes. The stools were watery, positive

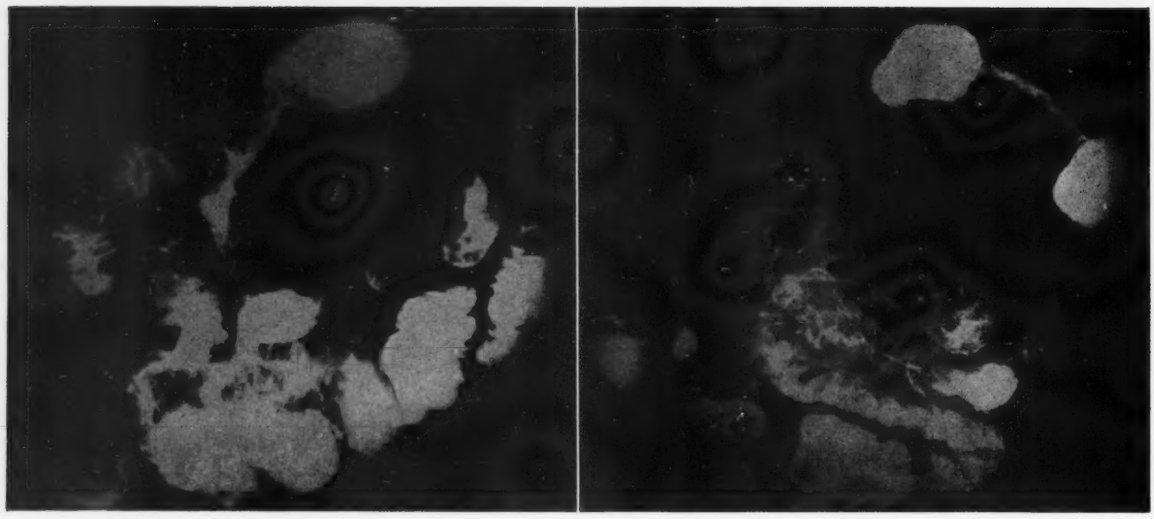
for guaiac, but not otherwise abnormal. Three weeks later he was discharged, improved. He went back to work and shortly thereafter suffered an attack of inflammation of the mandibular joints; clubbing of the fingers also became prominent during this period. He suffered intermittently from abdominal cramps and vomiting. In 1948 he was again hospitalized but this time because of gastrointestinal hemorrhage that required four transfusions within one week. In August, 1949, we were informed by his local doctor that he had suffered several episodes of melena and again required hospitalization. Associated with the acute hemorrhage was weakness of the cervical muscles, of an undetermined nature. Pigmentation of the skin developed but there was no laboratory evidence of adrenocortical insufficiency. The patient died suddenly in a local hospital of a severe intestinal hemorrhage, ten years after the onset of this progressive disease.

Autopsy revealed a dark brown pigmentation over the entire skin. The small gut was only 16 feet in length. Only scattered areas of normal-appearing mucosa were seen. There were many superficial erosions. Most of the mucosa was thickened and edematous with a granular and nodular hyperplastic configuration. In some segments the nodularity of the mucosa resulted in polyp formation. The terminal ileum exhibited the most advanced stages of the disease. Numerous areas of constriction due to marked fibrous tissue replacement were present. Histologic examination of the small bowel disclosed infiltration with numerous neutrophils and small round cells extending from the submucosa into the muscularis. Fibroblastic infiltration was intense in numerous areas. No tubercles were seen. The colon was normal but filled with blood clots. The lungs and adrenals were completely normal.

CASE II. A. D., thirty-three year old man, was seen in June, 1951, with a history of diarrhea and abdominal pain of twelve years' duration. The onset was acute with fever, periumbilical cramping and constipation. The illness was diagnosed as "intestinal flu." He was ill for fourteen days and then returned to work but suffered from extreme weakness. He ate irregularly and lost 15 pounds in the ensuing year. He was nervous, irritable, suffered from gas, indigestion, abdominal cramps and a diarrhea of four loose or watery, foul stools a day. There was no mucus or blood in the stools. He was admitted to a local hospital where a roentgen study was reported as negative and he was thereupon discharged with a diagnosis of vitamin B deficiency. He was better for four months but the weakness and diarrhea returned. Tonsillectomy was advised and performed but with no improvement. Repeated hospital admissions because of weakness and diarrhea were without much benefit. In 1942 ankle edema developed, especially when he was up and about. In 1944 the edema mounted to the thigh and buttocks and also involved the hands and eyelids. Renal function tests were normal. The edema was attributed to nutritional deficiencies and he was treated for the next two and a half years with weekly intramuscular injections. The diarrhea stopped, the stools became semisolid, the foul odor, the coated tongue, the anorexia, all disappeared. However, in 1945, despite continued therapy generalized edema recurred and kept him at home; it was associated with oliguria and left frontal headache. Several months following this, there was sudden onset of severe mid-abdominal pain with vomiting. The patient was admitted to a local hospital where a barium meal examination was said to reveal ileojejunitis.

During this hospital stay thrombophlebitis of the left saphenous veins developed. Hypoproteinemia at this time was marked, with a total serum protein of 3.2 gm. and an A/G ratio of 0.58, despite intensive plasma and amino acid infusions and high protein diet.

In 1945, at the age of twenty-seven, he was admitted to the Mt. Sinai Hospital with complaints of fever, abdominal cramps and diarrhea; his weight was 135 pounds. He appeared emaciated. The blood pressure was 80/65. The abdomen was distended and tympanitic. There was marked clubbing of the fingers and toes. Ankle edema was 3 plus. Laboratory work-up included 8.9 gm. hemoglobin, 3,500,000 red blood cells and 5,000 white blood cells with a normal differential. Total protein was 4.2 gm. per cent with an A/G ratio of 0.17; alkaline phosphatase was 13 King-Armstrong units, cholesterol 118 mg. per cent, potassium 4 mEq. and calcium 10.3 mg. per cent. Stool examination revealed fat and mucus. A glucose tolerance test showed a flat oral but a normal intravenous curve. Vitamin A determination revealed a fasting level of 358/100 ml. Administration of 25 mg. of testosterone daily was without



2A 2B

FIG. 2. A, small filling defects due to inflammatory polypi are visualized in several loops in the upper left abdomen. The loops of bowel are widely separated. B, the normal mucosal pattern is absent. A reticulated pattern is present in some areas and is due to extensive ulceration. Entero-intestinal fistulas are evident. The "string" sign is prominent. The dilated loops of ileum are also involved in the disease process. Diagnosis: Granulomatous ileojejunitis in the stenotic phase.

benefit. The patient was somewhat improved following the liberal administration of plasma, fluids and amino acids. During the last two years he drifted about to various institutions where he would be hospitalized for edema, treated with intravenous fluids and then discharged slightly improved. During this period he lost 30 pounds in weight.

Intensive study at another metropolitan hospital early in 1951 disclosed the following laboratory data. Urinalysis: specific gravity ranged from 1.004 to 1.028, occasional white blood cells and cast. Blood count: hemoglobin 11.5 gm. per cent, red blood count 3.5 to 4.5 million, white blood count 3.5 to 7.0 thousand, polymorphonuclear leukocytes 60 per cent, lymphocytes 35 per cent, eosinophils 3 per cent, monocytes 2 per cent. Erythrocyte sedimentation rate: 5. Hematocrit: 40. Reticulocyte count: 0.4–4.2 per cent. Stool: 2 plus guaiac, positive for trypsin. Total fat: 14.9 per cent. Fatty acids: 8 per cent. Vitamin A tolerance (figures are in percentages): fasting specimen—carotene 508, vitamin A 578; 3 hours—carotene 208, vitamin A 668; 6 hours—carotene 228, vitamin A 1,228; 9 hours—carotene 368, vitamin A 558. Glucose tolerance test: fasting specimen, 90 mg. per cent; 30 minutes, 130; 60 minutes, 155; 120 minutes, 150; 180 minutes, 80. Blood urea nitrogen 11 mg. per cent; total protein, 4.0 gm. per cent (albumin 1.8, globulin 2.2); icterus index, 2.9; total cholesterol 120 mg. per cent, free cholesterol 30 per cent; cephalin flocculation test, 0–2 plus; thymol turbidity test, 5.0–8.6; alkaline phosphatase, 3.4–4.2 Bodansky units; calcium, 6.7 mg. per cent; phosphorus, 4.3 mg. per cent; BSP, 30 minutes—15 per cent; 45 minutes—10 per cent. Prothrombin time, 20; control, 15. X-ray examination of the chest was reported as showing elevation of both diaphragms with atelectasis in both lung bases. A barium meal examination was said to show distortion and irregularity of the mucosal pattern of the third portion of the duodenum. The upper jejunum and the lower ileum presented areas of constricted and dilated segments with extensive irregularity of the mucosal pattern. The impression at the time was diffuse cicatrizing ileojejunitis.

In the past history of this patient there were strong elements of personality conflicts between the boy and his parents. He is the only child of an unmarried Italian Catholic woman. His father lives with a wife and five other children. The boy has always resented his father and has resisted his overprotective mother.

Physical examination at this time revealed an acutely ill individual. There was marked cheilosis and glossitis; the chest was flat to percussion over the right base with absent breath sounds. These signs were compatible with right hydrothorax. The heart was negative. The abdomen

was distended and presented a fluid wave. The edema was most striking in the lower extremities and the scrotum. All extremities revealed clubbing and cyanosis. Rectal examination was negative. Chvostek's and Trousseau's signs were negative. The blood count was essentially that found on previous examinations. Total serum protein was 3.8 gm. per cent with an A/G ratio of 0.52. Stool specimens were positive for occult blood. A barium meal examination revealed that the entire small bowel, starting at the ligament of Treitz, was involved in a granulomatous inflammatory process characterized by alternating areas of constriction and dilatation. The mucosal pattern in the constricted areas was completely altered, in some segments presenting a cast-like appearance and in others a reticulated design indicating diffuse, irregular ulceration. Multiple filling defects due to inflammatory polyps were evident in the constricted loops of bowel. Numerous short entero-intestinal fistulas were seen. The dilated segments also presented a complete absence of the normal mucosal pattern. Motility through the small bowel was extremely rapid. (Fig. 2.) The diagnosis was granulomatous ileojejunitis in the stenotic phase involving the entire small bowel.

SUMMARY

Two cases are presented of diffuse stenosing ileojejunitis involving the entire small bowel. One patient lived for ten years despite the extensive pathologic condition; the other is still alive more than twelve years after the onset of his progressively debilitating disease.

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Effect of Stilbamidine on Cutaneous Blastomycosis*

ADRIAN M. OSTFELD, M.D.

St. Louis, Missouri

IN the past few years a small number of patients with cutaneous and/or systemic blastomycosis has been treated with stilbamidine or related diamidine compounds. Stilbamidine,[1] stilbestrol[2] and propamidine[3] have all been used with favorable results and the evidence at hand indicates that these drugs represent the most effective ones available. Recently we have had the opportunity to observe a patient with cutaneous blastomycosis and to treat her with stilbamidine. The therapeutic response was excellent and it was thought worth while, therefore, to add this case to the small number previously reported.

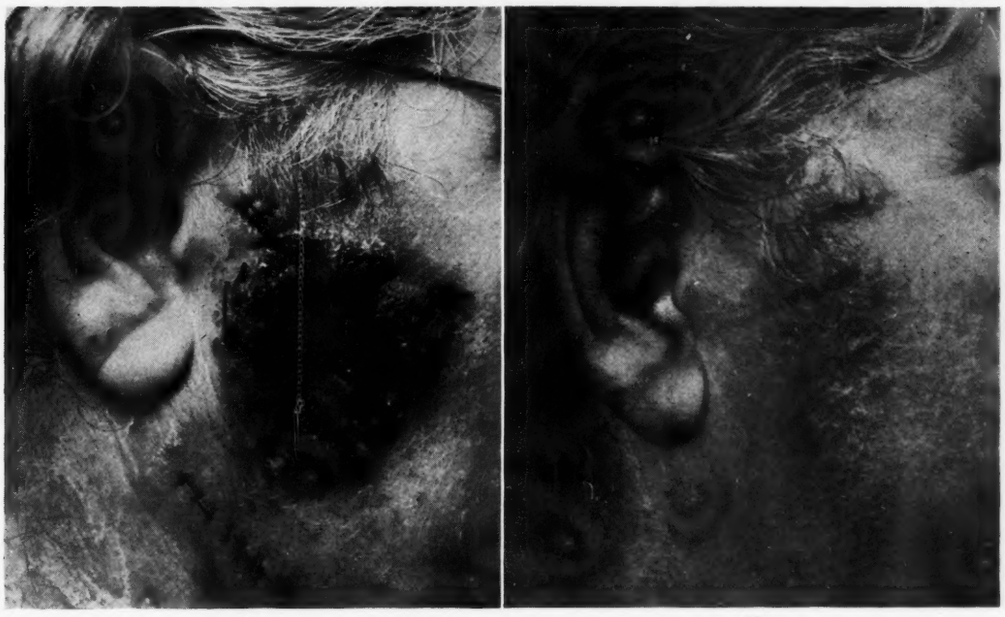
CASE REPORT

L. C. (B.H. No. 1-0-52-08698), a fifty-four year old white housewife, was admitted to the Ward Medical Service of the Barnes Hospital on September 23, 1952, because of a skin lesion of twelve weeks' duration. The patient had enjoyed good health until twelve weeks before entry, at which time she noted the appearance of a row of tiny, tender nodules on the right side of her face extending along the hair line from above the eye to the angle of the jaw. Although most of the lesions regressed in the following three weeks, one of them, located near the right malar eminence, increased slowly in size and became dark red in color and tender to touch. Four weeks prior to entry the lesion began to ooze; the secretion, initially serous, became serosanguineous. Concomitantly the involved area spread concentrically to involve the entire right malar region. The central portion ulcerated. Three weeks before admission a smaller nodule appeared beneath the angle of the right jaw. The patient consulted her physician who administered penicillin and streptomycin parenterally but this therapy was without effect. She was then referred to the Washington University Clinics where she was seen on September 16, 1952, in the plastic surgery clinic. It was thought that the facial lesion (Fig. 1A) was a basal cell carcinoma and a biopsy was performed. Histologic examination of the microscopic sections revealed both acute and chronic inflammatory changes with numerous giant cells. Hyperplasia of the epidermis with elongated anastomosing rete pegs was noted, and many organisms with refractile capsules, eosinophilic nuclei and intervening clear zones were seen. (Fig. 2.) Cultures from the lesions were positive for Blastomyces dermatitidis and the patient was admitted to the hospital. She had lived all her life in Missouri and Arkansas but careful questioning failed to indicate the source of the infection.

Physical examination revealed the patient to be a middle-aged, obese female who appeared quite comfortable. The vital signs were normal. There was a slightly raised, purple crusted lesion on the right cheek about 5 cm. in diameter, surrounded by a zone of erythema 5 mm. wide. Beneath the angle of the jaw two moderately firm, tender lymph nodes 1 cm. in diameter were palpable. The remainder of the physical examination was negative. A complete blood count was normal and urinalysis, stool examination and cardiolipin test were negative. Total and fractional serum proteins, and the erythrocyte sedimentation rate were also within normal limits. Roentgenograms of the chest and skull showed no abnormalities.

On September 27, 1952, stilbamidine therapy was begun, the patient receiving 50 mg. in 100 cc. of 5 per cent glucose in water intravenously. This daily dose was increased to 100 mg. and then to 150 mg. The latter dosage was continued until October 4th when the pa-

* From the Department of Internal Medicine, Washington University School of Medicine and the Barnes Hospital, St. Louis, Mo.



1A 1B

FIG. 1. A, before treatment; B, after stilbamidine was used.

tient began to complain of lightheadedness, which persisted for several hours after each infusion. For this reason and because the drug was in short supply, she was maintained on 100 mg. daily for nine subsequent days. Her course was otherwise uneventful except for mild nausea and vomiting, and progressive healing was observed. She was discharged in October and treated at home with 150 mg. of stilbamidine per day intravenously until November 26th. By that date the lesion was only 1 cm. in diameter and the previously involved area was covered with slightly hyperemic but otherwise normal skin.

The patient was again seen on January 5, 1953, at which time there had been additional regression although no more treatment had been given. A culture obtained on this date was negative. Because no further healing was evident in the ensuing three weeks, stilbamidine therapy in a dose of 150 mg. daily, intravenously, was again begun on January 30th and continued until February 21st. When the patient was examined on February 25th, the lesion had completely disappeared. (Fig. 1B.) The subcutaneous tissue was of normal consistency and the two lymph nodes at the angle of the jaw were no longer palpable. The patient felt well except that about February 1st, she experienced some numbness and tingling on the right side of her face. Examination showed moderate hypesthesia

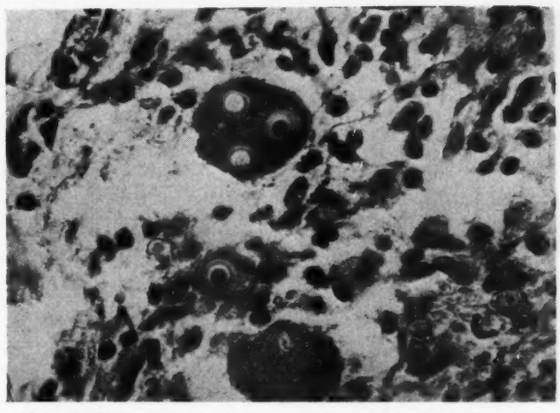


FIG. 2. Biopsy showing organisms within giant cells.

over the distribution of the three branches of the right fifth cranial nerve. By May 20th these findings had almost cleared and the patient was well.

In summary, progressive cutaneous blastomycosis of twelve weeks' duration was apparently eradicated by the action of stilbamidine administered intravenously over a three-month period. Early in the course of treatment nausea and vomiting were significant side effects. Later trigeminal nerve involvement with numbness of the right side of the face was present. However, both of these toxic effects, previously described by Snapper[4] and Collard and Hargreaves,[5] were transient and never severe enough to necessitate cessation of treatment. Thus

stilbamidine appears to present an effective method of treating patients with blastomyces infections which have previously been very resistant to therapy.

Acknowledgment: The stilbamidine used in this case was supplied through the courtesy of R. C. Pogge, M.D., of the William S. Merrell Company, Cincinnati, Ohio.

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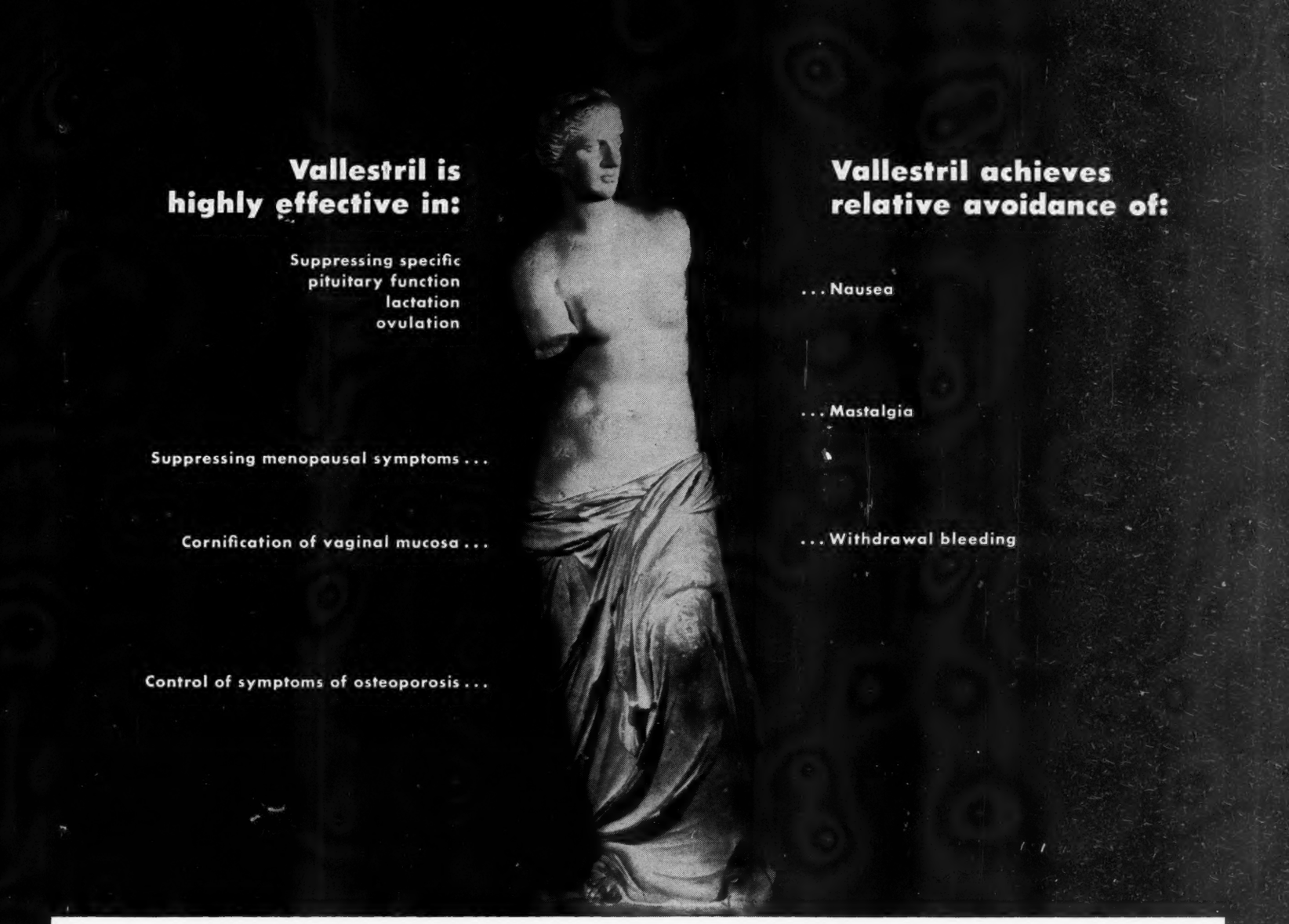

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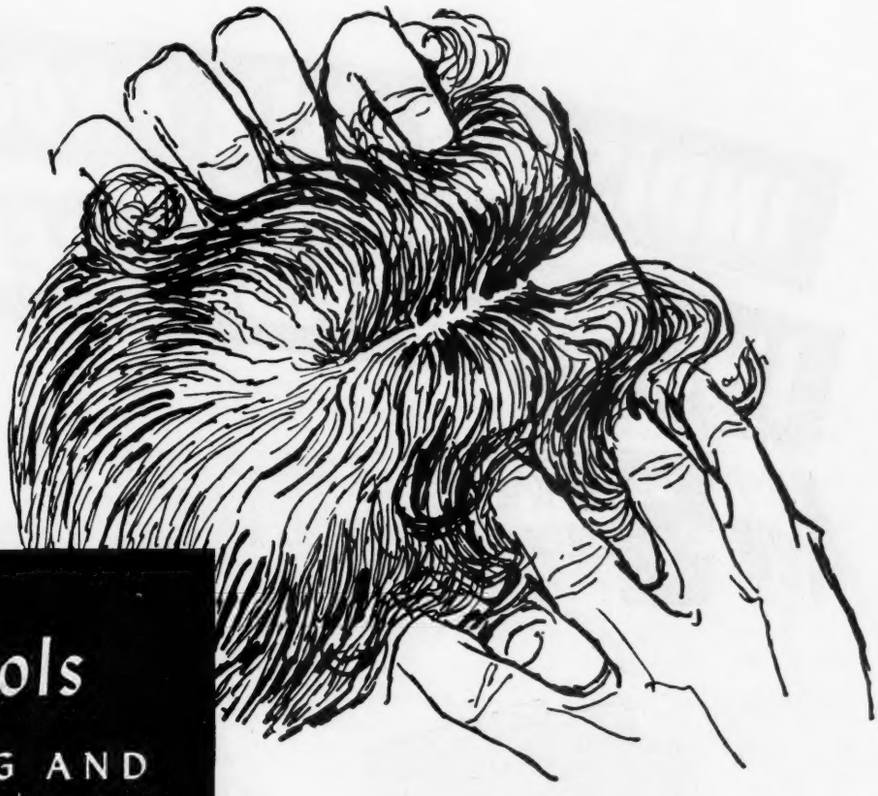

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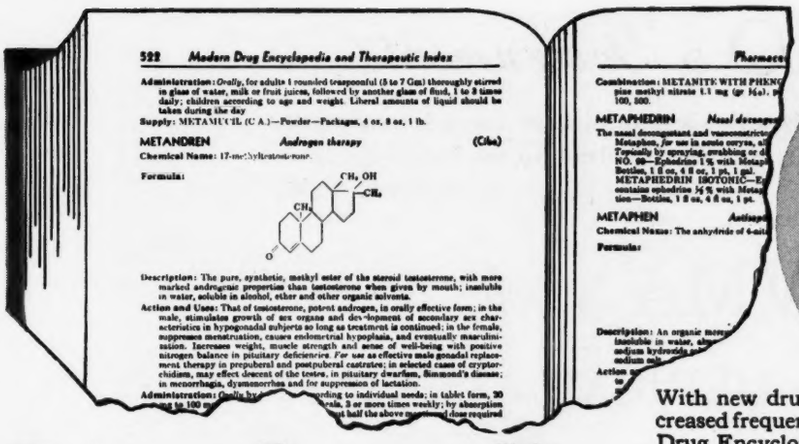

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GYNETONE REPETABS

Do you have all the facts on these

Important Anticonvulsants

TRIDIONE®

(Trimethadione, Abbott)

First successful synthetic agent—now agent of choice—for the symptomatic control of *petit mal*, myoclonic jerks and akinetic seizures.

PARADIONE®

(Paramethadione, Abbott)

Homologue to TRIDIONE. An alternate preparation which is often effective in cases refractory to TRIDIONE therapy. For treatment of the *petit mal* triad.

GEMONIL®

(Metharbital, Abbott)

A new drug of low toxicity for *grand mal*, *petit mal*, myoclonic and mixed seizures. Effective in conditions symptomatic of organic brain damage.

PHENURONE®

(Phenacemide, Abbott)

A potent anticonvulsant for psychomotor epilepsy, *grand mal*, *petit mal*, and mixed seizures. Often successful where all other forms of therapy have failed.

These are names to remember. Each, in turn, has signaled a dramatic advance in the field of antiepileptic medicine. Used properly, discreetly, these four drugs will add inestimably to the scope and progress of your treatment of various epileptic disorders. Write us today for literature on any or all of these important anticonvulsants. Abbott Laboratories, North Chicago, Illinois.

Abbott

1-165

A *Leeming* First:

the **New** *coronary vasodilator*

Metamine®

Leeming brand of triethanolamine trinitrate biphosphate

more effective in angina prevention

than other coronary dilators. When taken routinely, METAMINE prevents anginal attacks or greatly diminishes their number and severity. In addition, METAMINE is apparently nontoxic, even in prolonged or excessive dosage.

there is a reason

METAMINE is chemically distinct from all other organic nitrates in that it has a nitrogen, rather than a carbon linkage. This perhaps explains its greater effectiveness and freedom from side effects.

Dosage: METAMINE is effective in a dosage of **only 2 mg.** To prevent anginal attacks, swallow 1 METAMINE tablet after each meal, and 1 or 2 tablets at bedtime. Full preventive effect is usually attained after third day of treatment.

Supplied: METAMINE tablets, **2 mg.,** vials of 50.

Thos. Leeming & Co. Inc. 155 EAST 44TH STREET, NEW YORK 17, N.Y.

THE RECONSTRUCTIVE IRON TONIC.....

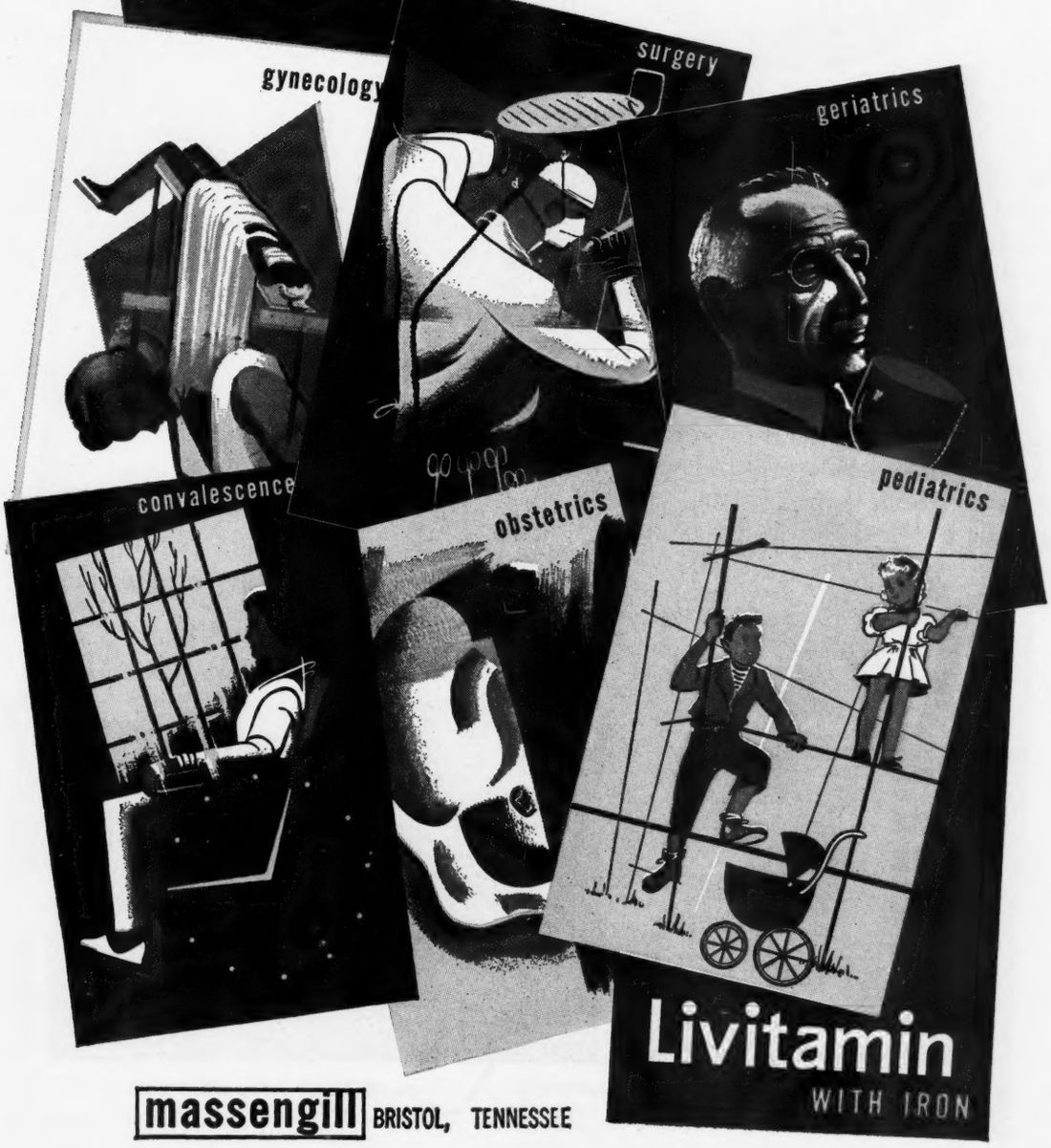
of wide application

Each fluidounce represents:	
Iron Peptonized (Equiv. in elemental iron to 70 mg.)	420 mg.
Manganese Citrate, Soluble	158 mg.
Thiamine Hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} (Crystalline)	20 mcg.
Niacinamide	50 mg.
Pyridoxine Hydrochloride	1 mg.
Pantothenic Acid	5 mg.
Liver Fraction 1	2 Gm.
Rice Bran Extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

Provides the multiple requirements for effective treatment of nonspecific asthenia.

The combined therapy is designed to increase appetite and improve the blood picture. Better digestion and improved anabolism are part of the corrective process.

Livitamin is designed to treat the entire syndrome



massengill BRISTOL, TENNESSEE

maximum convenience

Most diabetic patients can be controlled with appropriate diet and a single daily injection of

Globin Insulin

'B. W. & Co.'®

Intermediate action
Uniform potency
Clear solution

For complete dosage information please write

BURROUGHS WELLCOME & CO. (U. S. A.) INC.
Tuckahoe 7, New York

The small total dose required affords economy and virtual freedom from side actions.

MODERN MANAGEMENT

IN BRONCHIAL ASTHMA—

QUICK RELIEF

LONG-LASTING REMISSIONS

HP*ACTHAR Gel, subcutaneously or intramuscularly, gives quick relief in severe attacks of bronchial asthma, and may provide long-lasting remissions. Patients refractory to all customary measures, including epinephrine, and even to other forms of ACTH, may fully benefit from HP*ACTHAR Gel.

Used early enough, HP*ACTHAR Gel may become a valuable agent in prolonging the life span of asthmatic patients. ACTH "should not be withheld until the situation is hopeless".†

†Editorial, J. Allergy 23: 279-280, 1952.

THE ARMOUR LABORATORIES
CHICAGO 11, ILLINOIS
A DIVISION OF ARMOUR AND COMPANY

HP* ACTHAR *Gel* (IN GELATIN)

ACTHAR® IS THE ARMOUR LABORATORIES BRAND OF ADRENOCORTICOTROPIC HORMONE—CORTICOTROPIN (ACTH).

*HIGHLY PURIFIED

PHOTOGRAPH BY RUZZI GREEN

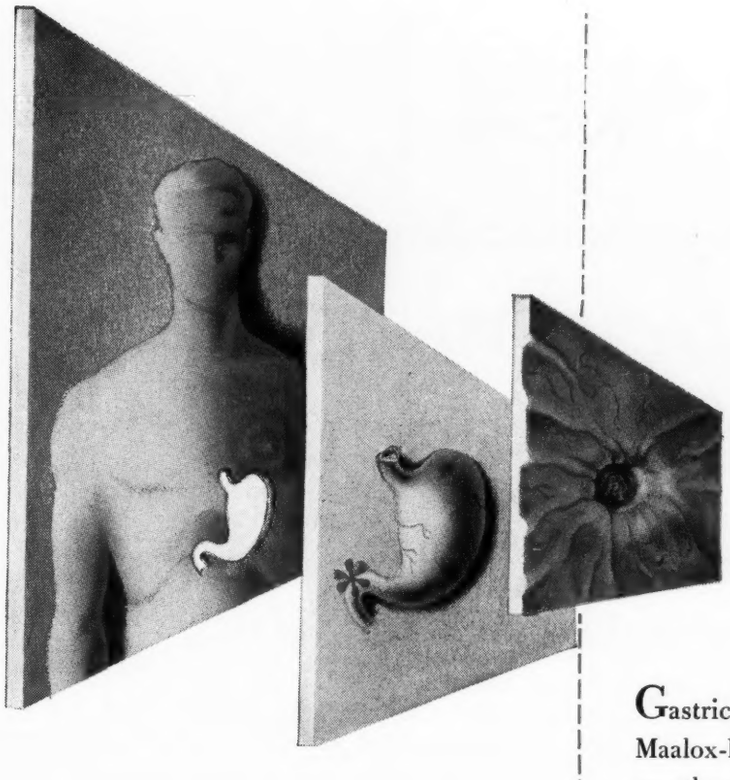
"My throat sure feels better"

TRACINETS®

BACITRACIN-TYROTHRICIN TROCHES WITH BENZOCAINE

ACTIONS AND USES: With TRACINETS you can readily relieve afebrile mouth and minor throat irritations in young patients—and in older ones, too. Acting together, bacitracin and tyrothricin are truly synergistic. Soothing local relief is afforded by benzocaine. In severe throat infections TRACINETS Troches, by their local action, supplement antibiotic injections.

QUICK INFORMATION: Each TRACINETS Troche contains 50 units of bacitracin, 1 mg. of tyrothricin and 5 mg. of benzocaine. Available in vials of 12.



maalox®

gives ulcer relief

without side effects

Gastric hyperacidity is controlled by Maalox-Rorer without constipation or other side effects commonly encountered with antacids. Relief of pain and epigastric distress is prompt and long-lasting. Available in tablets and liquid form.

Suspension Maalox-Rorer contains the hydroxides of Magnesium and Aluminum in colloidal form. The smooth texture and pleasant flavor make it highly acceptable, even with prolonged use.

Supplied: in 355 cc. (12 fluid ounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension Maalox.)

Samples will be sent promptly on request.

WILLIAM H. RORER, INC.

Drexel Bldg., Independence Square

Philadelphia 6, Pa.

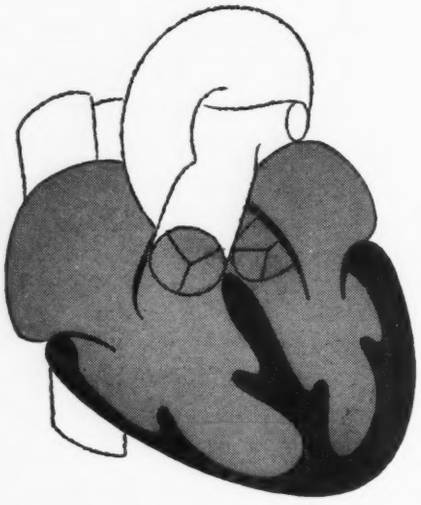
NOW

the first intramuscular digitoxin

DIGITALINE NATIVELLE®

INTRAMUSCULAR

for dependable digitalization and maintenance when the oral route is unavailable



DIGITALINE NATIVELLE INTRAMUSCULAR is indicated for patients who are comatose, nauseated or uncooperative, or whose condition precludes the use of the oral route.

DIGITALINE NATIVELLE INTRAMUSCULAR provides all the unexcelled virtues of its parent oral preparation.

Steady, predictable absorption.

Equal effectiveness, dose-for-dose with oral DIGITALINE NATIVELLE.

Easy switch-over to oral medication.

Clinical investigation has shown that DIGITALINE NATIVELLE INTRAMUSCULAR is "effective in initiation and maintenance of digitalization. A satisfactory therapeutic effect was obtained with minimal local and no undesirable systemic effects."*

DIGITALINE NATIVELLE INTRAMUSCULAR – 1-cc. and 2-cc. ampules, boxes of 6 and 50. Each cc. provides 0.2 mg. of the original digitoxin – DIGITALINE NATIVELLE.

*Strauss, V.; Simon, D. L.; Iglauer, A., and McGuire, J.: Clinical Studies of Intramuscular Injection of Digitoxin (Digitaline Nativelle) in a New Solvent, Am. Heart J. 44:787, 1952.

Literature and samples available on request.

VARICK PHARMACAL COMPANY, INC.
(Division of E. Fougera & Co., Inc.)
75 Varick Street, New York 13, N. Y.

the realization of a hope . . .

a new physio-chemical complex that consistently and significantly reduces elevated serum cholesterol levels.

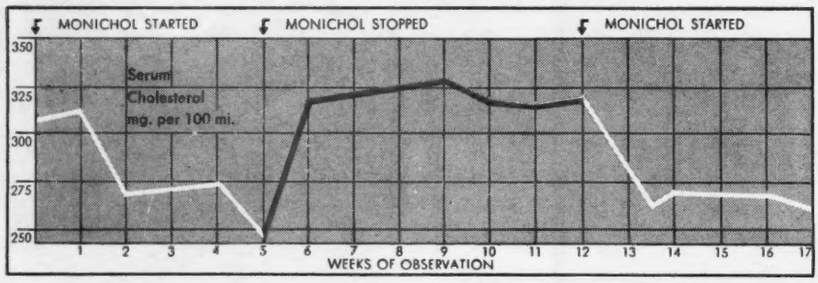
MONICHOL*

I.V.C®

This typical response of an idiopathic hypercholesteremic patient to an uninterrupted daily intake of Monichol — an entirely non-toxic medication — shows a significant drop from 306 mg. to 240 mg. per 100 ml. of serum cholesterol after five weeks of medication.†

The investigators† stress the need for continued administration of Monichol because idiopathic or familial hypercholesteremia is most probably an *inborn error of metabolism.*

Uninterrupted Daily Intake of Monichol
Essential in the Management of Hypercholesteremia



Please note the *prompt rise of the serum cholesterol to pre-treatment levels* when medication was stopped. We, therefore, urge you to ask your patients to have their prescriptions refilled as soon as their supply is exhausted.

Indications: For the therapeutic and prophylactic management of hypercholesteremia so frequently associated with cardiovascular disease and diabetes.

Dosage: The recommended dosage of 1 teaspoonful four times or two teaspoonfuls twice daily after meals is both the minimum and the optimum dosage.

Formula: Each teaspoonful (5 cc.) contains:

Polysorbate 80	500 mg.
Choline Dihydrogen Citrate	500 mg.
Inositol	250 mg.

Supplied: Bottles of 12 oz.

†Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. *152*:682 (June 20) 1953. *Trademark

Monichol normalizes cholesterol metabolism

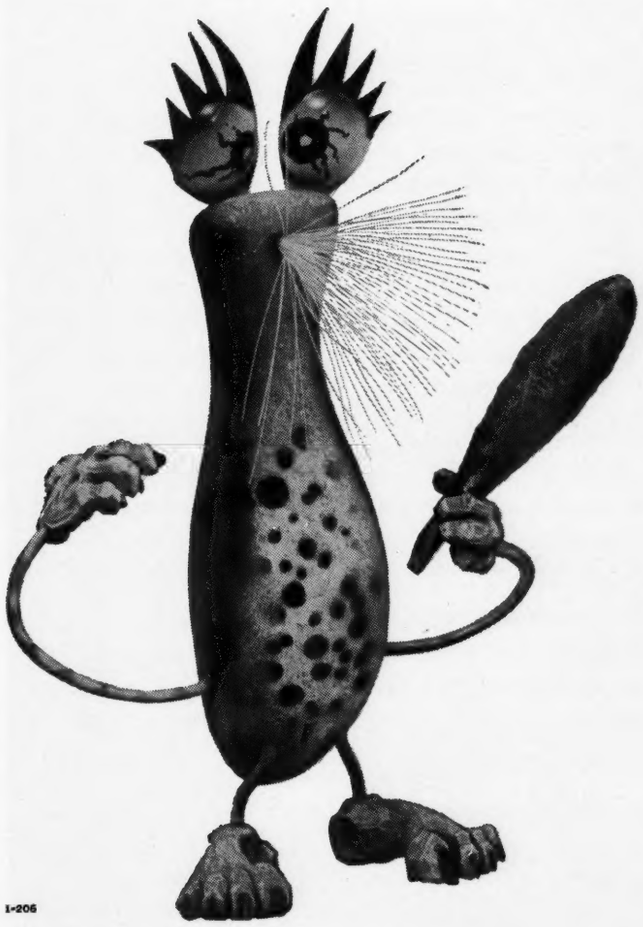
IVES-CAMERON COMPANY, INC., 22 East 40th Street, New York 16, N. Y.

Against STAPHylococci, STREPtococci and PNEUMOcocci

ALWAYS CONSIDER

*ERYTHROCIN**

a selective antibiotic



1-206

ORALLY EFFECTIVE
against these coccic infections—especially indicated when patients are allergic to penicillin and other antibiotics or when the organism is resistant.

A DRUG OF CHOICE
against staphylococci—because of the high incidence of staphylococci resistant to other antibiotics.

A DRUG OF CHOICE
because it does not materially alter normal intestinal flora; gastrointestinal disturbances rare; no serious side effects reported.

ADVANTAGEOUS
because the special acid-resistant coating developed by Abbott, and Abbott's built-in disintegrator, assure rapid dispersal and absorption in the upper intestinal tract.

USE ERYTHROCIN
in pharyngitis, tonsillitis, scarlet fever, pneumonia, erysipelas, osteomyelitis, pyoderma and other indicated conditions.

Abbott

* Trade Mark
Erythromycin, Abbott
Crystalline

Gantrisin 'Roche' —
a single, soluble,
wide-spectrum
sulfonamide —

Gantrisin 'Roche' is especially soluble at the pH of the kidneys. That's why it is so well tolerated... does not cause renal blocking... does not require alkalies. Produces high plasma as well as high urine levels. Over 150 references to Gantrisin® in recent literature.

A new, potent antibacterial—

Gantricillin-300 'Roche'

... for wide-spectrum antibacterial therapy. Each Gantricillin®-300 tablet provides 300,000 units of penicillin PLUS 0.5 Gm of Gantrisin®-- the single, soluble sulfonamide.

Pneumonia weather...
the season
for bacterial
respiratory tract
infections

a time
for...

TERRAMYCIN®

BRAND OF OXYTETRACYCLINE

The value of Terramycin in promptly controlling otitis media, severe sinusitis, laryngotracheobronchitis, bacterial pneumonia and virtually all infections of the respiratory tract, due to or complicated by the many organisms sensitive to Terramycin, is now a matter of clinical record.

Because of its excellent toleration and rapid response, Terramycin is a therapy of choice for bacterial respiratory tract infections. Among the convenient dosage forms of Terramycin are Capsules, Tablets (sugar coated), good-tasting Oral Suspension, non-alcoholic Pediatric Drops, Intravenous for hospital use in severe infections and various topical preparations including Troches, Nasal and Aerosol for adjunctive therapy.

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.

Conclusive evidence

of the effectiveness and low toxicity

of Furadantin

in treating bacterial urinary tract infections

is provided in its recent

acceptance by the Council

FURADANTIN®

brand of nitrofurantoin

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

The N.N.R. monograph on Furadantin states:

EATON LABORATORIES Inc.
NORWICH, NEW YORK

"**Nitrofurantoin.—Furadantin (Eaton).—**

Actions and Uses.—Nitrofurantoin, a nitrofuran derivative, exhibits a wide spectrum of antibacterial activity against both gram-positive and gram-negative micro-organisms. It is bacteriostatic and may be bactericidal to the majority of strains of Escherichia coli, Micrococcus (Staphylococcus) pyogenes albus and aureus, Streptococcus pyogenes, Aerobacter aerogenes, and Paracolobactrum species. The drug is less effective against Proteus vulgaris, Pseudomonas aeruginosa, Alcaligenes faecalis, and Corynebacterium species; many strains of these organisms may be resistant to it. However, bacterial resistance to other anti-infective agents is not usually accompanied by increase in resistance of the organisms to nitrofurantoin. The drug does not inhibit fungi or viruses.

Nitrofurantoin is useful by oral administration for the treatment of bacterial infections of the urinary tract and is indicated in pyelonephritis, pyelitis, and cystitis caused by bacteria sensitive to the drug. It is not intended to replace surgery when mechanical obstruction or stasis is present. Following oral administration, approximately 40% is excreted unchanged in the urine. The remainder is apparently catabolized by various body tissues into inactive, brownish compounds that may tint the urine. Only negligible amounts of the drug are recovered from the feces. Urinary excretion is sufficiently rapid to require administration of the drug at four to six hour intervals to maintain antibacterial concentration. The low oral dosage necessary to maintain an effective urinary concentration is not associated with detectable blood levels. The high solubility of nitrofurantoin, even in acid urine, and the low dosage required diminish the likelihood of crystalluria.

Nitrofurantoin has a low toxicity. With oral administration it occasionally produces nausea and emesis; however, these reactions may be obviated by slight reduction in dosage. An occasional case of sensitization has been noted, consisting of a diffuse erythematous maculopapular eruption of the skin. This has been readily controlled by discontinuing administration of the drug. Animal studies, using large doses administered over a prolonged period, have revealed a decrease in the maturation of spermatozoa, but this effect is reversible following discontinuance of the drug. Until more is known concerning its long-term effects, blood cell studies should be made during therapy. Frequent or prolonged treatment is not advised until the drug has received more widespread study. It is otherwise contraindicated in the presence of anuria, oliguria, or severe renal damage.

Dosage.—Nitrofurantoin is administered orally in an average total daily dosage of 5 to 8 mg. per kilogram (2.2 to 3.6 mg. per pound) of body weight. One-fourth of this amount is administered four times daily—with each meal and with food at bedtime to prevent or minimize nausea. For refractory infections such as Proteus and Pseudomonas species, total daily dosage may be increased to a maximum of 10 mg. per kilogram (4.5 mg. per pound) of body weight. If nausea is severe, the dosage may be reduced. Medication should be continued for at least three days after sterility of the urine is achieved."

In infectious and allergic rhinitis and sinusitis

Biomydrin "is effective as an antibiotic in clearing the nose of pathogenic organisms and purulent secretions. In many cases, sterile cultures were obtained after a brief period of treatment."

Antibiotics & Chemotherapy *3*:299 (March) 1953.

Improvement in 113 of 124 Patients*

Diagnosis	Number of patients	Improved
Chronic catarrhal rhinitis	11	11
Chronic allergic rhinitis	26	25
Right maxillary sinusitis	2	1
Chronic naso-pharyngeal catarrh	6	6
Chronic suppurative sinusitis	3	3
Coryza, Head cold, Catarrhal rhinitis	58	51
Influenza	2	1
Acute catarrh	4	3
Hypertrophic rhinitis	12	12
TOTAL	124	113 (91.1%)

* Eye, Ear, Nose and Throat Monthly *32*:512 (Sept.) 1953.

BIOMYDRIN

'BIOMYDRIN' AND 'THONZONIUM BROMIDE' ARE TRADEMARKS OF NEPERA CHEMICAL CO., INC.

The Biomydrin formula

THONZONIUM BROMIDE 0.05%. Synthesized in the Nepera laboratories. Exceedingly potent antibacterial. Greatly enhances the antibiotic activity of neomycin and gramicidin. Reduces surface tension, facilitating spreading and penetrating. Mucolytic.

NEOMYCIN SULFATE 0.1%. Effective against gram-positive and gram-negative organisms.

GRAMICIDIN 0.005%. Effective against gram-positive organisms.

PHENYLEPHRINE HCl 0.25%. Widely preferred vasoconstrictor.

THONZYLAMINE HCl 1.0%. *Therapeutic concentration* of this effective antihistaminic aids in controlling local allergic manifestations.

- Prompt, prolonged shrinkage of nasal mucosa without secondary congestion.
- pH is 6.2. Isotonic and buffered.
- Does not interfere with ciliary activity.
- Spray covers larger area than could be reached by drops.
- Available on prescription only.

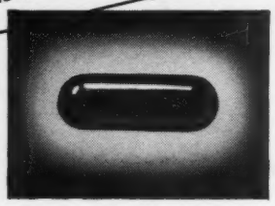
DOSAGE: Adults—2 or 3 sprays in each nostril; 4 or 5 times a day as needed, or as directed by physician. Children—1 or 2 sprays in each nostril; 4 or 5 times a day as needed, or as directed by physician.

Nepera Chemical Co., Inc. Pharmaceutical Manufacturers, Yonkers 2, N. Y.

COMPARISON OF CRYPTENAMINE WITH PROTOVERATRINE AND THREE OTHER VERATRUM ALKALOID PREPARATIONS

DRUG	Emetic: Therapeutic Ratio	Therapeutic Index
Cryptenamine—Irwin-Neisler	4:1	125
Protoveratrine A & B	1:1	20
Commercial Veratrum Alkaloid Preparation A	1.2:1	40
Commercial Veratrum Alkaloid Preparation B	1:1	
Commercial Veratrum Alkaloid Preparation C	1:1	

*Another * reason why*



THERE IS NO *SAFER* PREPARATION FOR THE TREATMENT OF HYPERTENSION

Veratrite® brings your hypertensive patients the best therapeutic benefits of Veratrum, since it provides Cryptenamine * the newly isolated, broader safety-ratio Veratrum alkaloid developed through Irwin-Neisler research.

Sustained control of blood pressure, with minimum side reactions and maximum safety, is the significant contribution of Veratrite to the long-term management of hypertension.

Each tabule contains:

Whole-powdered Veratrum viride (*containing Cryptenamine*) . . . 40 C.S.R.† Units

Sodium Nitrite . . . . 1 grain

Phenobarbital . . . . ¼ grain

Carotid Sinus Reflex

Supplied: *Bottles of 100, 500, 1000.*

Veratrite

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

Major advance in dermatitis control:

The new direct approach to the control of dermatitides is hormonal, enlisting the antiphlogistic and antiallergic potency of compound F—foremost of the corticosteroid hormones.

The new objective is adapting corticoid therapy to simple inunction treatment, and obtaining relief in various forms of dermatitides within days —sometimes within hours.

The new attainment is Cortef Acetate Ointment, which rapidly controls edema and erythema, halts cellular infiltration, arrests pruritus in such harassing skin problems as atopic dermatitis, contact dermatitis, pruritus vulvae and ani, neurodermatitis, and seborrheic dermatitis.

Cortef*

Acetate Ointment

Supplied: *Cortef Acetate Ointment is available in 5 Gm. tubes in two strengths—2.5% concentration (25 mg. per Gm.) for initial therapy in more serious cases of dermatitis, and 1.0% concentration (10 mg. per Gm.) for milder cases and for maintenance therapy.*

Administered: *A small amount is rubbed gently into the involved area one to three times a day until definite evidence of improvement is observed. The frequency of application may then be reduced to once a day or less, depending upon the results obtained.*

*TRADEMARK FOR UPJOHN'S BRAND OF HYDROCORTISONE.

A product of Upjohn Research *for medicine...produced with care...designed for health*

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

Advertisers' Index

November, 1953

for your
peptic ulcer
patients...

Antrenyl™
bromide

New High Potency
Anticholinergic with
No Bitter Aftertaste

As adjunctive therapy in your standard peptic ulcer regimen*, Antrenyl offers potent anticholinergic action to inhibit motility of the gastrointestinal tract and gastric secretion.

Although Antrenyl is one of the most potent of all anticholinergic agents, it rarely causes esophageal or gastric irritation and has no bitter aftertaste. In individualized doses, it is well tolerated and side effects are absent or generally mild.

In one study[1] patients receiving Antrenyl obtained relief from acute symptoms within 24 to 36 hours. Dosage was individually adjusted at 5 to 10 mg. four times a day. Side effects were considered less pronounced than those of other similar agents ordinarily used in the management of peptic ulcer.

Prescribe Antrenyl in your next case of peptic ulcer and spasm of the gastrointestinal tract. Available as tablets, 5 mg., scored, bottles of 100; and syrup, 5 mg. per teaspoonful (4 cc.), bottles of 1 pint.

Ciba Pharmaceutical Products, Inc., Summit, N. J.

*Leading gastroenterologist recommends:
rest
sedation
antacids
gastrolitating diet
anticholinergics

1. Rogers, M. P., and Gray, C. L.: *Am. J. Digest. Dis.* 19:180, 1952.